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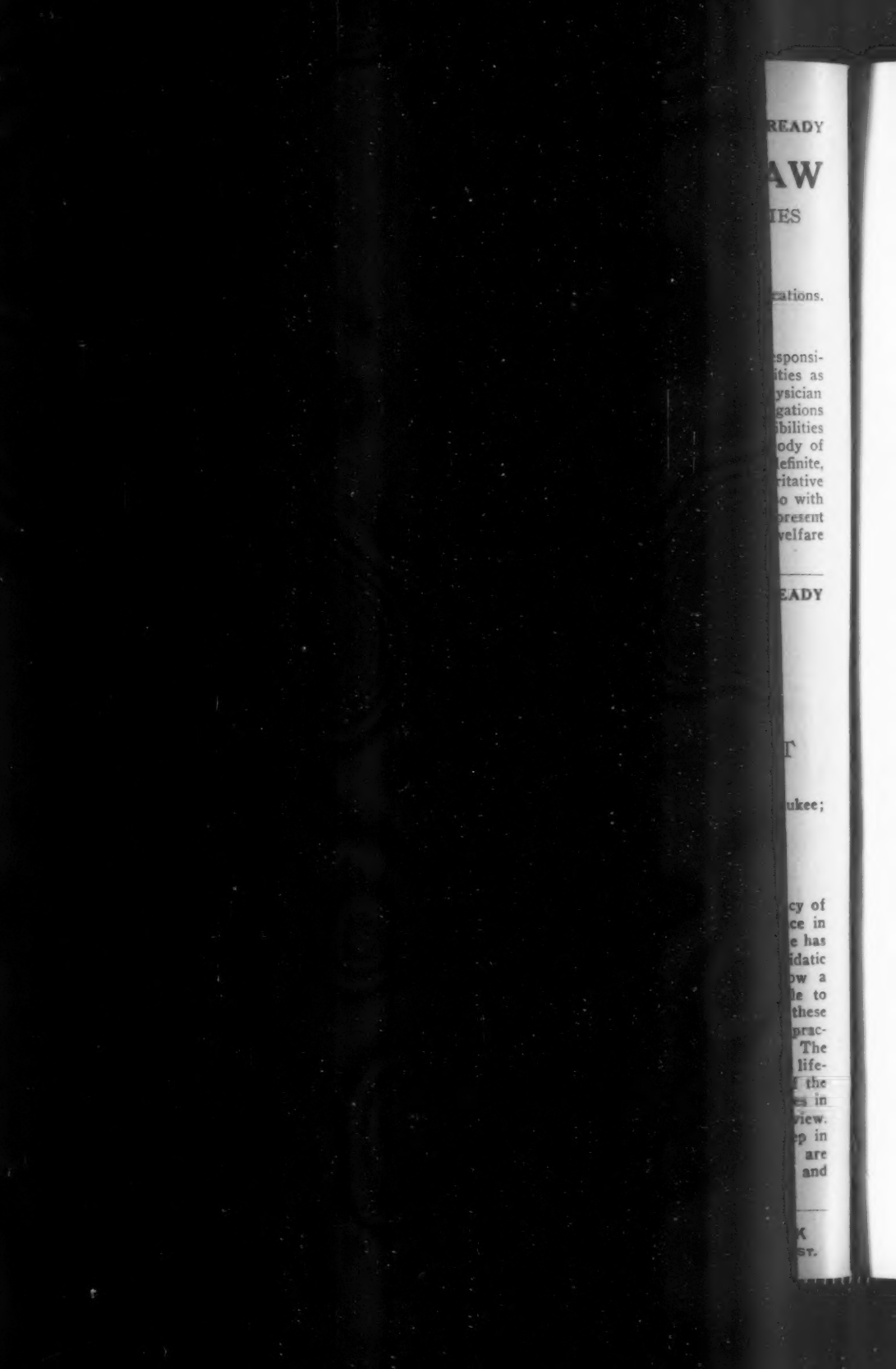

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THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1913

ORIGINAL ARTICLES

SOME OF THE DISPUTED PROBLEMS ASSOCIATED WITH SURGERY OF THE LARGE INTESTINE.

By William J. Mayo, M.D.,

SURGEON TO ST. MARY'S HOSPITAL, ROCHESTER, MINNESOTA.

Much can be learned concerning the underlying causes of diseases of the large intestine by studying the changes which have been incident to the development of its function. In the adult human the large intestine appears as a continuous whole, yet functionally it is sharply delimited at the point of vascular anastomosis between the derivatives of the superior and inferior mesenteric vessels at the splenic flexure. The first half of the large intestine is derived from the same embryologic sources as is the small intestine, and has a similar important metabolic function. About 50 per cent. of the fluids and 10 per cent. of the solids are absorbed in this part of the large intestine. Beyond the splenic flexure absorption is limited in amount, the bulk of absorbable material placed in the rectum being promptly passed into the proximal colon for absorption.

It has been shown by Bond,[1] Cannon,[2] and others that there is a fairly constant antiperistalsis in the large intestine which passes material back toward the cecum.

The study of comparative anatomy in the herbivorous demonstrates the enormous absorptive value of the cecum. Lyle[3] has aptly compared its storage function to the stomach. Unlike the stomach which absorbs but a small amount, the cecum absorbs actively. In some animals there is a sphincter in the ascending

[1] Med. Rec., August 12, 1905, 246–252.
[2] Amer. Jour. Phys., 1898, i, 359.
[3] British Med. Jour., 1906, ii, 238.

colon to hold the material in the cecum. In man a marked physiological activity is shown at this point, although no colic sphincter exists.

The portion of the duodenum which lies between the pylorus and the opening of the common duct may be said to be the vestibule of the small intestine, the food passing rapidly through to reach the area of absorption. In a general way the same conditions exist in the descending colon, which also acts as a vestibule through which food refuse passes rapidly to reach the storage chamber of the sigmoid. The splenic flexure of the colon is held high, as a mechanical means of maintaining food products as long as possible in the first half of the large intestine. This method of retention is more economic in its operation than a muscular sphincter apparatus would be. Some sixty years ago Rokitansky[4] called attention to the fact that the descending colon was usually found empty at autopsy, just as the *x*-ray bismuth picture today so often shows it in the living, and which is so often misinterpreted as evidences of supposed stricture.

In an article written in 1900[5] I called attention to a contraction of the ileocecal orifice as a cause of certain intestinal phenomena, and pointed out that many cases of constipation might have their origin in metabolic changes in the small intestine rather than in the large. This helps to explain the obstinate constipation which sometimes continues after an ileosigmoidostomy, although such stasis is largely due to the fact that the material from the ileum as it enters the sigmoid passes backward by an antiperistalsis into the first half of the large intestine and then pursues its ordinary course much as though ileosigmoidostomy had not been done. This has been demonstrated in the *x*-ray findings following ileosigmoidoscopy in some of our cases.

The sigmoid varies greatly in its length, size, and position because it is a late development without fixed characteristics (Finney[6]). This is further shown in the weakness of its walls, which in the middle and later decades of life so frequently permit hernias of the mucosa through the musculature. These hernias or diverticula are an important factor in the causation of localized peritonitis from diverticulitis, as well as occasionally the chronic irritating focus in initiating cancer of the sigmoid.

The rectosigmoid juncture is at the third sacral vertebra, and here nature has again introduced certain mechanical obstacles to prevent the too ready discharge from the storehouse of the sigmoid into the rectum. So often a well-trained nurse asks, "Shall I give a high injection with the colonic tube into the colon or a low rectal?" The result, of course, is quite the same. The colonic

[4] Handbuch der spec. path. Anat., 1842.
[5] Mayo, Annals of Surgery, September, 1900.
[6] Trans. Amer. Surg. Assoc., 1908, xxvi, 475–516.

tube pushed through the anus out of sight lies coiled in the rectum when it is supposed to be in the colon. Such a tube cannot often be made to pass through the rectosigmoid in this manner.

The rectum is not normally a fecal storehouse, although through habit it often becomes so, especially in the female. Examination of the male for service in the army shows the rectum to be empty normally.

Bands of adhesions are often developed during adult life. At the time of birth the cavity of the omentum is obliterated as high as the transverse colon. The process continues until in adult life points of adhesion are found as high as the pyloric end of the stomach, which obliterate the lesser cavity of the peritoneum to a greater or less degree. Similar conditions may exist between the omenta and the gall-bladder, and may be taken as evidence of infection. Various observers have asserted that the adhesions which sometimes exist between the epiploic tags of the sigmoid and the abdominal wall, etc., are of great importance, and always the result of pathological conditions; yet such adhesions will be found in a certain percentage of necropsies on subjects over forty years of age, who during life showed no symptoms ascribable thereto.

Jackson[7] has called attention to the veil of adhesions so often present between the ascending colon and the abdominal wall as a cause of pathological symptoms. We can at least say safely that this condition, like the others mentioned, is developmental in origin. The cecum does not reach its normal situation until about the time of birth, therefore the attachment between this late arrival and its fixed place of abode is recent, and resembles adhesions of a peculiar pannus type. The weakness of this attachment on the right side is partially instrumental in permitting the prolapse of the cecum into the pelvis. Wilms[8] believes this prolapse to be of great pathological significance in producing cecal stasis. "Lane's kink" is undoubtedly also of developmental origin, and due to a fixation by bands of the terminal three inches of the ileum. The important question is, Do these conditions produce symptoms, or are they merely anatomical deviations without pathological meaning?

The transverse colon averages in length from 20 to 22 inches, and has 10 or 11 inches distance to travel from the hepatic to the splenic flexures. Its supporting attachments in the centre are to the movable stomach, therefore prolapsus of the transverse colon is common. There is little else it can do. The length of the transverse colon serves a physiological purpose in picking up the final remnants of nutritive material. The *x*-ray photograph taken with the patient in the standing position, with the weight of the bismuth in the stomach or in the transverse colon, or both, pro-

[7] Surg., Gyn., and Obst., 1909, ix, 278–287.
[8] Arch. d. klin. Chir., 1903, lxix, 795–842.

duces an exaggeration of this normal condition. How often can we say that it is truly pathological?

If the small bands of adhesions which are found in one case, such as a sigmoidepiploic tag attachment to the abdominal wall, be productive of so much harm in one patient, how can we expect that another patient with similar symptoms will be benefited by the bands of adhesions which the surgeon purposefully forms to hold up a prolapsed organ like the cecum? How much of truth and how much of fancy is embodied in the elucidation of this subject no one can say. That it is most obscure we all agree. One group of observers is convinced that the whole thing is mechanical and the result of some type of infection rather than an error of development. Another group contents itself with the belief that these patients are all neurasthenics, although they are less ready to give an opinion as to the cause or nature of the condition. That many of the patients operated on have been greatly benefited cannot be denied, yet if one were to take the case histories and reports of successful treatment by means of such mechanical therapy and put them all in a hat to be picked out at random, one could not determine from the histories of the patients those who had been relieved of symptoms by operating for a mobile cecum, for relief of the adhesions, for mobility of the sigmoid, for fixation of the sigmoid, for prolapse of the stomach, and, for that matter, for movable kidney. The histories read alike, but the operations seem to vary with the bias of the operator. Are all of these deductions wrong? Have the profession in regular medicine with their accurate observations no conclusions which depend upon more authentic data? To say that relief of symptoms demonstrates the truth of the opinion is not sufficient unless we grant the same privilege to the mental healers.

I think we can agree with Arbuthnot Lane that metabolic changes may take place in the large intestine, which in some cases produce symptoms of disease and that absorbable toxic products are responsible for many of the symptoms which are spoken of in a general way as gastro-intestinal neurosis, intestinal toxemia, intestinal stasis, putrefactive intoxication, etc.

It is probable that the first part of the colon, and especially the cecum and ascending colon, will be found at fault. To it is delegated the difficult function of culling out the last nutritive remnants from the now infected mass of food. Carcinoma of the cecum and ascending colon are often accompanied by the most profound anemia in cases without glandular or general metastasis. We not infrequently see a removable tumor and a perfect cure follow an operation upon a patient so anemic that the hemoglobin runs as low as 30 and the reds in the vicinity of 2,500,000. Many such patients have been left to die because this specific anemia was believed to be a cachexia from hopeless malignant metastasis.

This same anemia may accompany tuberculous tumor of the cecum of the hypertrophic variety without ulceration to explain it, but is not found to accompany tumors of the sigmoid even though there may be sloughing.

It is possible that all of these mechanical conditions have some effect in detaining the infected remnants of food too long in the absorbing half of the colon, the symptoms being due to the effect of the toxic products absorbed on the controlling sympathetic ganglia. That the theory of mechanical causation alone is insufficient explanation is established by the fact that, as a rule, none of the ordinary results of mechanical obstruction exist, such as muscular hypertrophy of the wall of the bowel, etc. Quite the opposite condition exists—the bowel is thin walled and ballooned, the patients showing marked evidence of loss of sympathetic balance of the neurasthenic type, resembling in some respects a mild Graves' disease from hyperthyroidism.

The views of Arbuthnot Lane,[9] Rovsing,[10] Coffey,[11] Jackson, and others should receive careful consideration. Whether or not the particular operations advocated by these surgeons are ultimately found to be correct, at least their work has called the attention of the profession to an important and heretofore neglected field, and offers a possible explanation of the cause of the protean symptoms in a large group of patients who have received much treatment and little benefit from the medical profession, and who have been exploited by the dietetic fadist and the charlatan.

THE RELATION OF ANAPHYLAXIS TO IMMUNITY AND DISEASE.[1]

By Victor C. Vaughan, M.D.,

PROFESSOR OF HYGIENE AND PHYSIOLOGICAL CHEMISTRY IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR.

Studies of the phenomena of protein sensitization, so-called anaphylaxis, have given us quite a new idea of many of the problems of immunity and disease. The only way in which cells of any kind—bacterial, protozoal, or animal—can grow and multiply is by elaborating ferments which split up the pabulum within their reach, thus preparing a food supply. The cell which can no longer supply a digestive ferment is already dead, whatever be the kind

[9] Surg., Gyn., and Obst., February, 1908, 115.
[10] Samml. klin. Vortr., 1906, xv, No. 431.
[11] Annals of Surgery, January, 1907, 43–49.
[1] Read at the Fifteenth International Congress of Hygiene and Demography, September, 1912

or amount of pabulum surrounding it. The cell which supplies only such ferments as cannot digest the food supply within its reach dies immediately. This is the fundamental fact of the general immunity possessed by higher animals against the lower forms of life. As was shown in my laboratory some years ago, there is no constant and fixed relation between the toxicogenic and pathogenic properties of bacilli. The Bacillus prodigiosus contains enough intracellular poison to kill guinea-pigs when injected intraperitoneally in doses of 1 to 90000 body weight, while the anthrax bacillus requires 1 to 1700, and still the former is non-pathogenic and the latter highly pathogenic. The explanation lies in the fact that the prodigiosus cannot grow and multiply in the animal body, because its secretions do not digest the proteins of the animal body, or, what is more probable, the secretions of the body cells destroy the bacillus. On the other hand, the anthrax bacillus elaborates ferments which do digest the proteins of the animal body, while the body cells do not destroy the bacillus, and thus serve the microörganism with food. For these same reasons a given bacillus may be pathogenic to one species or to one race and wholly devoid of effect on other animals. Furthermore, the virulence of different strains of the same microörganism varies with the abundance and the strength of the digestive ferment. One strain of the pneumococcus may not kill guinea-pigs in less doses than 1 c.c. of a twenty-four-hour culture, while another may kill in one-millionth of this amount, and still when animals inoculated with the two strains are dead the same number of bacilli or the same amount of bacillary cell substance will be found in both. One strain has multiplied a million times faster than the other, because of the greater abundance and effectiveness of the secretions which enable it to grow.

The great lesson which we have learned from our studies of anaphylaxis is that the digestive secretions of body cells may be developed and modified by the kind of protein brought into contact with them. When a foreign protein is introduced into the animal body certain cells develop a specific digestive ferment which splits up that protein and no other. Cellular digestion is a physiological process and it is normally specific inasmuch as the secretion of each kind of cell splits up the pabulum in such a way as to supply the needs of its own cell, but the pabulum upon which the cells of the body normally feed consists of the proteins of the blood and lymph. From these sources all the cells of the body select their food material through the agency of their digestive ferments. Normally there is much preparation of the foods upon which the cells of the animal body feed. The proteins taken into the alimentary canal are broken up by the digestive juices into amino acids and in this process they loose all their distinctive character. During absorption or soon thereafter the amino acids are put together again, but now so grouped as to form the proteins peculiar to the species.

From the special proteins, thus prepared, each kind of body cell obtains its nutriment. Parenteral digestion is a physiological process in which the material acted upon, the cleavage agents and the assimilating cells are constant. However, even with all this preparation of food for the body cells it must happen at times that foreign proteins, as such, find their way into the blood and lymph. In order to digest this unusual pabulum the body cells elaborate a specific ferment, which digests this protein and no other. This is one of the fundamental and central facts of protein sensitization.

The second fundamental fact in protein sensitization is that every protein molecule contains a poisonous group. This is true of all bacterial, vegetable, and animal proteins so far as they have been investigated. The poisonous group in the protein molecule is the same so far as its physiological action is concerned, whatever be the nature of the entire molecule of which it is a part. Chemically there must be differences in the poisonous groups of different protein molecules, but, as has been stated, in physiological action one cannot be distinguished from another. It may be that more exact studies will show slight variations in physiological effect. I have designated the poisonous as the primary group in the protein molecule. I have also suggested that it be regarded as the "archon" or keystone of the protein molecule. It probably contains the benzol ring with nitrogenous side chains. Attached to this primary group are secondary groups which may be designated as the "characteristic" groups, because it is in these that one protein differs from another. The sensitizing properties of proteins reside in the secondary groups, because it has been shown that these when freed from the poisonous group may sensitize animals to the unbroken molecule. It is for this reason that the special ferments elaborated in the cells of the animal under the influence of a foreign protein are specific. The poisonous group, when detached from its secondary or characteristic groups, does not sensitize either to itself or to the whole protein from which it came. In the original protein molecule the poisonous group is rendered inert physiologically by being combined with the secondary groups. In its free state it becomes a poison on account of the avidity with which it disrupts other protein molecules and combines with their secondary groups. The protein molecule may be compared to a basic or neutral salt, and it becomes more and more poisonous as its basic elements are removed, and when the free acid only is left, its maximum toxic action is reached. The protein poison is a powerful agent. In the purest form in which I have been able to obtain it, and this probably is far from chemical purity, it kills guinea-pigs of from 200 to 300 grams weight, when injected intracardiacly in doses of 0.5 milligram. When used intra-abdominally this dose must be multiplied by 16, and when given subcutaneously, by about 32. These differences in effect according

to the method of administration are of importance and are accounted for by the fact that the poison attacks and is neutralized by the body proteins with which it first comes in contact.

Whenever neutral proteins undergo cleavage as the result of the activity of proteolytic enzymes, there are steps in the process, when the activity of the poisonous group is made more manifest and this proceeds as the basic elements are stripped off. In this way the poison is in part liberated in alimentary digestion. Biedl and Kraus have shown that the action of the anaphylactic poison and that of pepton are identical. This is necessarily true because the active group in both is the same. The protein poison is set free or activated by the alimentary proteolytic enzymes, and if it were a readily diffusible substance all proteins would be poisonous to man when taken by the mouth. But since it does not speedily pass through the alimentary walls and since additional cleavage renders it inert we escape its poisonous action. In parenteral digestion of proteins there are no walls to prevent the diffusion of the poison, and consequently more or less injury always results.

Anaphylactic shock is such a striking phenomenon that for a long time it obscured the essential facts of protein sensitization and led investigators far astray. When compared with immunity the two seemed antipodal; in one the life of the animal is saved; in the other it is jeopardized and in the majority of instances lost. Indeed, it was a misconception which led Richet to select the term "anaphylaxis." I still hold to the following statements concerning protein sensitization first formulated by Wheeler and myself.[2]

1. Sensitization consists in developing in the animal a specific proteolytic ferment which acts upon the protein that brings it into existence and on no other.

2. This specific proteolytic ferment stored up in the cells of the animal as a result of the first treatment with the protein remains as a zymogen until activated by a second injection of the same protein.

3. Our conception of the development of a specific zymogen supposes a rearrangement of the atomic groups of the protein molecules of certain cells in the animal body or an alteration of the molecular structure. In other words, we regard the production of the specific zymogen not as the formation of a new body, but as resulting from an alteration in the atomic arrangement within the protein molecule and a consequent change in its chemism.

4. Some proteins in developing the specific zymogen, produce profound and lasting changes in molecular structure, while the alterations induced by others are slighter and of temporary duration, the molecular structure soon returning to its original condition.

[2] Jour. Infect Dis., 1907, iv 476.

5. Bacteria and protozoa are living, labile proteins; while egg-white, casein, serum albumin, etc., are stable proteins. The proteins of the one group are in an active, and those of the other in a resting state, but both are essentially proteins, made up of an acid or poisonous chemical nucleus and a basic or non-poisonous group. The former in its effects upon animals is the same whether derived from the living or the dead protein, and the latter in the one instance induces specific immunity and in the other specific susceptibility; but the immunity and susceptibility each consists in developing in the animal body the capability of splitting up a specific protein. If the living protein be split up before it has time to multiply sufficiently to furnish a fatal quantity of the poison the animal lives and we say that it has been immunized. If the stabile protein be introduced into the animal it leads to the development of a specific proteolytic ferment, and if enough of it to supply a fatal dose be reinjected after this function has been developed, the animal dies. The first or sensitizing dose of egg-white injected into an animal is digested just as surely as is the second, but the process goes on so slowly that we see no effect, but in fact the first dose has affected the animal profoundly, so profoundly that the change wrought in certain cells of the animal body persist for months, possibly for years, and may be transmitted from the mother to her offspring. We do not say that the animal is sensitized unless some immediate and striking effect follows our treatment, but this is wrong. An immediate effect, especially a fatal issue, on reinjection, depends upon the rapidity with which the protein is split up and its poisonous constituent set free. The sensitizing injection leads to the development of a specific enzyme and the protein of this injection is so slowly digested that the poison set free at any one time is not sufficient to produce any recognizable effect. If time enough be allowed between the sensitizing and the reinjection for the accumulation of a large amount of the specific enzyme, then the protein is split up promptly and anaphylactic shock and death result. These views concerning protein sensitization first offered in 1907, have been on the whole, confirmed by later investigators.

The fact that an animal is sensitized before the time when a reinjection is followed by anaphylactic shock has been conclusively demonstrated by inducing passive anaphylaxis with serum taken from animals in the so-called preanaphylactic state. Likewise it has been shown that serum taken from animals in the so-called antianaphylactic state passively sensitizes fresh animals.

The Prevention of Anaphylactic Shock. From a practical standpoint anaphylactic shock is the least important of the phenomena of sensitization. It is always an artificially induced condition, and the only importance it brings to the practitioner is that he should know how to prevent it in serum therapy. Although the

procedure necessary to protect the patient against anaphylactic shock was first pointed out by Vaughan, Jr., the best work along this line has been done by Besredka. The last-mentioned investigator has shown that the intraperitoneal injection of from $\frac{1}{50}$ to $\frac{1}{100}$ c.c. of the serum in sensitized guinea-pigs renders them so positively refractory that five hours later intracerebral injections are wholly without effect. Besredka has made quite a thorough study of the means by which anaphylactic shock in serum therapy may be averted and he states his conclusions as follows:

1. Preparatory heating of therapeutic sera to 56° tends to suppress the phenomena of sensitization without wholly averting them. Besredka states that all therapeutic sera prepared at the Pasteur Institute are subjected to this temperature, and that instances of anaphylactic shock are less frequent, and, when seen, less severe in France than in countries in which this preliminary heating is not practised.

2. Alcoholic and ether narcosis give a complete, but transitory, immunity to anaphylactic shock. (This is not practical.)

3. Preventive injections of serum heated to 80° produce a certain and lasting immunity, but it develops slowly and is accompanied by slight reaction. (It will be understood that only that portion of the serum used to prevent anaphylactic shock is heated to this temperature, which would render antitoxin inert.)

4. The best method of averting anaphylactic shock is either by rectal injection of the unheated serum, or better still, by the subcutaneous injection of a very small dose.

The recommendation of Vaughan, Jr., is that in all cases in which anaphylactic shock may be feared a preliminary injection of from 0.1 to 0.2 c.c. should be made, and after an interval of two hours, provided no untoward symptoms have appeared, the full dose may be given. The suggestion is made by Rosenau and Anderson that all individuals who have shown any tendency to asthma, together with those who have received previous injections of the serum, with an interval of twelve days or longer, should be included among those in whom anaphylactic shock may be feared. It is not held that even with these precautions all the symptoms of serum disease will in all cases be averted, but serious anaphylactic shock is not likely to occur.

Serum Disease. The studies of v. Pirquet and Shick[3] on diseased conditions induced by therapeutic sera have proved of great value in explaining the phenomena of protein sensitization. In a certain percentage of individuals who receive injections of horse serum for the first time certain well-defined symptoms develop, usually from six to twelve days after the injection. The symptoms consist of fever, more or less general edema and rash, generally urticarial,

[3] Die Serumkrankheit, 1905.

though sometimes erythematous. The rash is usually accompanied by intense itching and it may cover not only the entire surface of the body but extend to the visible mucous membrane of the mouth and throat, about the anus, and into the rectum. The lymph glands may be enlarged, and pain in the joints is often severe. The percentage of persons thus affected by the first dose of horse serum increases with the quantity of serum employed. The explanation offered by v. Pirquet is that some of the unchanged serum remains in the body until sensitization is sufficiently developed to "bring the effects of the toxic body up to the level of clinical observation." This demonstrates that a reinjection is not necessary in order to develop the state of protein sensitization. The evolution of the specific enzyme begins soon after the introduction of the foreign protein and gradually proceeds, and the liberation of the protein poison increases parri passu. It is not until the effects of the liberated poison approach the "level of clinical observation" that we recognize them, but this is not at the beginning of the process. Sensitization of the body cell probably begins as soon as the foreign protein comes in contact with it. The foreign protein so impresses the body cell that the latter undergoes such changes in its intramolecular structure that it elaborates a new and specific enzyme. The fact that soluble proteins sensitize so much more promptly and efficiently than suspensions renders it probable that cellular penetration is essential to the most thorough effect. The additional fact that relatively dilute solutions sensitize more promptly and more efficiently than more concentrated ones suggest that degree of molecular concentration has some influence upon the processes of sensitization.

Von Pirquet and Shick observed two kinds of reaction in those who received reinjections after intervals of twelve days or longer. In some the reaction is of the same character as that described above, but it appears two or three days earlier. It is supposed that those in whom this form, designated as "accelerated reaction," occurs, have partially passed beyond the condition of sensitization, but easily resume it on receiving the reinjection. There seems to be no danger to life in either the "delayed" or "accelerated reaction." The one accompanied by marked danger to life is the "immediate." In this the effects manifest themselves within a few hours, often within a few minutes, after the reinjection. These individuals are in a fully sensitized condition, and it is in these that anaphylactic shock should be feared.

There are instances in which the first injection of horse serum has induced alarming, and rarely fatal, anaphylactic shock. These have been reported with sufficient frequency to cause more or less anxiety in the employment of therapeutic sera; besides, it raises the very important question as to why a small percentage of persons should be, apparently naturally, susceptible to an agent

to which the great majority are immune. Cases of "horse asthma," in which more or less violent symptoms, such as sneezing, inflammation of the conjunctiva and the mucous membrane of the upper air passages result from riding behind horses are well known. The flying hairs from horses carrying minute quantities of protein are inhaled and may cause local sensitization, and it may be that this accounts for the instances of anaphylactic shock observed after first injections of horse serum. The recent brilliant work of Rosenau in which he has shown that the expired air contains a protein sensitizer seems to explain sensitization to horse serum.

Vaccination. The valuable research of von Pirquet[4] on vaccinia has done much to elucidate the problems of sensitization. By daily vaccinations this investigator has shown that the process is accelerated until finally it passes through every phase in a few hours.

This explains not only the development of vaccinia and the way in which it protects against smallpox, but also vaccination in other infectious diseases. The avirulent organism of vaccinia still has the protein constitution of the virulent one of smallpox. It has been modified in function but not seriously altered in essence by its passage through the cow. The proteins constituting its molecules have not been changed, or if at all, so slightly altered that one form still sensitizes to the other. The modified virus sensitizes the body cells and by this we mean that it causes the cell to elaborate a specific enzyme that digests and destroys the virus. The body cells retain this new function and when the smallpox virus finds its way into the body it is digested and destroyed before it has time to multiply sufficiently to cause disease. This is the basis of all bacterial and protozoal vaccination. In securing his vaccine for chicken cholera Pasteur modified the organism by successive growths on artificial culture media. That for anthrax he obtained by growth at relatively high temperature, and that for rabies by drying the cord. The vaccine for typhoid fever is obtained by the use of cultures killed by heat. All these processes in the special instances modify the proteins of the organisms so slightly that they still sensitize to themselves. This is protein sensitization and gives protein immunity. It is wholly different from toxin action and toxin immunity and we should not confuse the two by discussing one in terms of the other. In protein immunity there is no antigen and no antibody, and we will proceed more understandingly if we stop employing these terms in discussing protein sensitization. The toxins are either ferments or closely related bodies, and the substance that digests the protein on reinjection or in the sensitized state of the animal is a ferment, and it is proper to speak of it as consisting of amboceptor and complement, but further

[4] Klinische Studien über Vakzination u. Vakzinale Allergie, 1907.

than this the nomenclature introduced by the genius of Ehrlich to explain toxin action and reaction has no place in the literature of sensitization.

If what has been stated be true, protein sensitization is a most important factor in acquired immunity and it will be well to discuss methods of using so powerful an agent in combating disease. It should always be held in mind that every protein contains a powerful poison, and that no unbroken protein can be injected into the body without carrying with it this poison, and moreover, the parenteral digestion of a protein means that its poisonous group will be set free or activated in the body. The liberation of this poison occurs not in the alimentary canal, the walls of which may protect the body or from which it may be rejected by vomiting or purging, or by both, but in the blood and tissue, and there is no escaping its effects. It is a poison, not a toxin, and there is up to the present time no known antidote for it. The indiscriminate employment of protein injections now being made should be most positively condemned.

Work done in my laboratory indicates that with some proteins at least the sensitizing and poisonous groups may be separated, and that when this is done the former sensitizes quite as efficiently and sometimes much better than the unbroken protein containing its poisonous group. In animals the non-poisonous part of the typhoid protein gives immunity to the living bacillus to a much greater degree and more promptly than the unbroken bacillus, either alive or dead. It is freely soluble and the more soluble protein sensitizers are the more promptly and efficiently do they act. However, this needs more thorough study and tests should be made on man.

That the tuberculous animal behaves differently from the non-tuberculous on receiving injections of the tuberculin protein, whether it be in the form of the living bacillus, in dead cells, or in solution, has been abundantly demonstrated. Before Koch gave us tuberculin, Aloing and Courmont had come to the conclusion that the tubercle bacillus produces soluble substances which reduce the natural resistance of the body and render it more susceptible to reinfection. This corresponds closely with the first impression made by observation of the phenomena of anaphylaxis; the impression that led Richet to select this term. In 1891, Koch described a perfect example of protein sensitization as we understand it today. He stated that when a healthy guinea-pig is inoculated with the living tubercle bacillus there is no change at the site of inoculation until from ten to fourteen days later, when a hard lump forms, finally opens and ulcerates, and continues until the animal dies. On the other hand, when a tuberculous guinea-pig is inoculated with the living bacillus, on the second or third day a lump forms, soon becomes necrotic, falls out, ulcerates for

a time, and finally, heals without any infection of the neighboring lymph glands. In 1897, Trudeau observed that when healthy rabbits receive injections of virulent cultures in the eye, there is little to be seen for about fourteen days, when with increasing vascularity tubercles form in the iris after which inflammation extends and the eye is practically destroyed within from six to eight weeks. Like treatment of tuberculous rabbits develops an iritis within from two to five days, but at the end of the second or third week at a time when the controls begin to develop destructive changes the inflammation begins to subside. Later studies have confirmed and amplified these, and it has been found that death may be induced within twenty-four hours by injecting a large amount of a living culture into a tuberculous animal.

The same difference between healthy and tuberculous animals has been observed in their response to injections of dead cultures of the tubercle bacillus. The first observation along this line, so far as I know, was made by Strauss and Gamaleia, who found that when large numbers of dead tubercle bacilli are injected into tuberculous animals death results, while similar amounts are without immediate effect upon healthy animals.

When we come to tuberculin, every phase of its action or its failure to act is explainable on the ground that the tuberculous animal is a sensitized one. Koch found that 0.5 gram of his preparation killed tuberculous guinea-pigs, and induced no symptoms in healthy ones. A fraction of 1 milligram may cause marked symptoms in a tuberculous man, while many times this amount is borne easily by a healthy man. The inflammatory reaction about local tubercular lesions caused by injections of tuberculin is explained by the fact of the high degree of sensitization in their localities, and the cleavage of the bacilli. The ophthalmic, cutaneous, subcutaneous, and intravenous tests with tuberculin are all typical sensitization reactions. Even in the failure to respond to tuberculin seen in advanced tuberculosis we have the condition known as antianaphylaxis, which simply means that the anaphylactic ferment is exhausted by the large amount of material supplied by the bacilli in the body.

There is another line of evidence that in tuberculosis there is a condition of specific protein sensitization. This is to be found in the fact that this disease is much more deadly in lands and among people who have recently come under its influence than it is where it has prevailed for many generations. In other words, the widespread and long-continued existence of the disease, slowly, and at the cost of much sickness, and many deaths, brings a certain degree of immunity. The readiness with which the North American Indian has succumbed to this disease is a striking illustration, and Calmette has recently collected additional evidence on this point. He states that tuberculosis is being widely disseminated

among peoples who have until recently been free from it. The world-wide wanderings of the white man are carrying the disease to every people, from the Laplander and Esquimaux of the Arctics to the negroes and Malays of the tropics. Iceland, the Faro Islands, and the steppes of Russia are being infected, and in these new regions tuberculosis exists in its most speedily fatal forms. The same author points out that recently discovered methods for the recognition of this disease, even in latent states, shows that among Europeans not more than 7 or 8 per cent. reach more than twenty years of age without receiving the infection. Those who survive the first infection become more or less immune, and after that develop when they do acquire the disease the more chronic forms.

Römer[5] concludes that the less widely tuberculosis is distributed among a people the greater is the case mortality, and the wider the distribution the smaller is the case mortality.

Still another fact of importance is that the most speedily fatal forms of tuberculosis, such as the miliary and meningeal, are more frequent among children than among adults.

There is another matter of much importance in this connection which we must discuss. We have found the tubercle bacillus highly resistant to lytic agents, and it appears that its long experience as a parasite has led it to protect itself with deposits of wax and fat, but proteolytic enzymes digest the most firm proteins. Friedberger has found that at least some strains of this bacillus are digested by the serum of healthy guinea-pigs, and the researches of Markl, Bail, and Kraus and his students have shown that tubercle bacilli placed in the peritoneal cavity of tuberculous animals respond to Pfeiffer's reaction. Some strains are dissolved in the peritoneum of healthy guinea-pigs, but dissolution occurs more promptly and more completely in the peritoneum of a tuberculous animal. The healthy animal may have to depend upon its phagocytes to combat the invading bacillus, but the tuberculous animal supplies a specific proteolytic enzyme, and to this the fresh invader succumbs.

Nature is slowly immunizing the white man to tuberculosis, and the question arises whether or not the process employed by nature can be aided in any way. There is before the medical profession at this time no greater question than this: Is it possible to aid in eradicating tuberculosis by vaccination? As Römer says, the problem of securing immunity to tuberculosis with a non-infective virus is of great practical importance and recent work brings the possibility of doing this more and more to the front. What we need is a vaccine. Various methods of modifying the tubercle bacillus so that it could be used as a vaccine have been tried. The bovo vaccine of von Behring was tried, but the increased resistance given by it was found to be of short duration.

[5] Beiträge z. klinik. d. Tuberk., 1912, xxii, 301.

Attempts to reduce its virulence by age, heat, chemicals, and by submitting it to ultraviolet and other rays and emanations have been made. What we need is a tubercle protein sensitizer. It should be soluble, and it should be free from the poisonous group in the protein molecule. In my opinion the nearest approach to this desired substance is the non-poisonous portion of the tubercle protein. So far we have not been able to secure a uniform product. Some preparations seem to fill every requirement. They sensitize animals to the unbroken bacillus, dead or alive, and in surface tuberculous lesions they cause inflammation about the tuberculous area, and we have seen the tuberculous tissue slough off and complete recovery result; but other preparations made from the same cellular substance by the same method seem inert. We have had similar difficulties with the sensitizing groups from other proteins. Some preparations from egg-white sensitize to unbroken egg-white, while others seem wholly without effect, and still all are prepared from the same material and in the same way. Evidently the sensitizing group in the protein molecule is a highly labile body and susceptible to influences which so far we have not been able to recognize. We have no difficulty in obtaining the poisonous group uniformly, but it is otherwise with the sensitizing body. Further work along this line is needed, and if an efficient and uniformly reliable sensitizer for the tubercular protein, free from the poisonous group, can be secured, all children should be vaccinated for tuberculosis; then with protection against natural infection the restriction of tuberculosis will be as completely under man's control as is that of smallpox. It should be clearly understood that the protection afforded by vaccination is relative and not absolute.

The studies inaugurated by Wright have demonstrated that vaccination is of service not only in prevention, but also in cure. Bacteria and protozoa are particulate, and in many diseases they are confined to limited localities. As we have seen, sensitization may also be local. No body cell is sensitized against a foreign protein until the latter comes in contact with the former and penetration of the body cell is probably essential to the most efficient sensitization. The microörganisms of acne are located in the cutaneous tissue and being particulate and not in solution, the area sensitized by them is small, if there be any sensitization at all. By vaccine therapy the area of sensitization is greatly extended and the amount of lytic agent formed and made available is greatly increased. This being in solution and diffusible, digests and destroys the bacteria located in the skin. The same is true of the treatment of localized tuberculosis, or of any other localized infectious disease. In vaccine therapy, as in vaccination, the great need is for soluble sensitizers free from poisonous content. When these are secured, and not until then, we may develop a vaccine therapy along scientific lines, and expect to secure important results with it.

Fever. It is interesting and instructive to read the older literature on fever in the light of the knowledge which has been gained in the study of sensitization. It has long been known that the parenteral introduction of proteins in small amounts and especially repeated introduction, leads to fever. The older literature on this subject as well as an account of his own work was given in 1883 by Roques.[6] In 1888, Gamaleia[7] showed quite clearly that fever accompanies and results from the parenteral digestion of bacterial proteins, and a year later Charrin and Ruffer[8] confirmed this work and extended it to non-bacterial proteins. In 1890, Buchner[9] produced the characteristic phenomena of inflammation—color, rubor, tumor, and dolor—by the subcutaneous injection of diverse bacterial proteins. In 1895, Krehl and Matthes[10] induced fever by the parenteral introduction of albumoses and peptons, but they did not obtain constant results, which we now know are secured only by regulation of the size and frequency of the dosage. In 1909, Vaughan, Wheeler, and Gidley[11] demonstrated that any desired form of fever—acute fatal, continued, intermittent, or remittent—can be induced in animals by regulating the size and frequency of the doses of foreign protein administered parenterally, and in 1911, Vaughan, Cumming, and Wright[12] extended the details of this work. These investigators established the following points:

1. Large doses of unbroken protein administered intra-abdominally, subcutaneously or intravenously, have no effect upon the temperature; at least, do not cause fever.

2. Small doses, especially when repeated, cause fever, the forms of which may be varied at will by changing the size and the interval of dosage.

3. The effect of protein injections on the temperature is more prompt and marked in sensitized than in fresh animals.

4. The intravenous injection of laked blood corpuscles from either man or the rabbit causes in the latter even in very small quantity, either in single or repeated doses, prompt and marked elevation of temperature.

5. Laked corpuscles after removal of the stroma by filtration have a like effect.

6. Protein fever can be continued for weeks by repeated injections, giving a curve which cannot be distinguished from that of typhoid fever.

7. Protein fever is accompanied by increased nitrogen elimination and gradual wasting.

8. Protein fever covers practically all cases of clinical fever.

[6] Substances Thermogenes, Paris, 1883.
[7] Ann. de l'Institut Pasteur, xii, 229.
[8] Comp. Rend. Soc. de Biol., 1889, 63.
[9] Berl. klin. Woch., 1890, 216.
[10] Arch. f. exp. Path. u. Pharm., 1895, xxxv, 232.
[11] Jour. Amer. Med. Assoc., August 21, 1909.
[12] Zeitsch. f. inner. Medizin, ix, 458; Trans. Assoc. Amer. Physicians, 1911.

9. Animals killed by experimentally induced fever may die at the height of the fever, but as a rule, the temperature rapidly falls before death.

10. Fever induced by repeated injections of bacterial proteins and ending in recovery is followed by immunity.

11. The serum of animals in which protein fever has been induced digests the homologous protein *in vitro*.

12. Fever results from the parenteral digestion of proteins.

13. There are two kinds of parenteral proteolytic enzymes, one specific and the other non-specific.

14. The production of the non-specific ferment is easily and quickly stimulated.

15. The development of the specific ferment requires a longer time.

16. Sensitization and immunity are different manifestations of the same process.

17. Foreign proteins, living or dead, formed or in solution, when introduced into the blood soon diffuse through the tissues and sensitize the cells. Different proteins have predilection places in which they are deposited and where they are, in large part at least, digested, thus giving rise to the characteristic symptoms and lesions of the different diseases.

18. The subnormal temperature which may occur in the course of a fever or at its termination is due to the rapid liberation of the protein poison, which in small doses causes an elevation, and in larger doses a depression of temperature.

19. Fever *per se* must be regarded as a beneficent phenomenon, inasmuch as it results from a process inaugurated by the body cells for the purpose of ridding the body of foreign substances.

20. The evident sources of excessive heat production in fever are the following: (*a*) That arising from the unusual activity of the cells supplying the enzyme; (*b*) that arising from the cleavage of the foreign protein; (*c*) that arising from the destructive reaction between the split products, from the foreign protein and the proteins of the body.

In 1910, Friedberger[13] studied the effects of graduated doses of foreign proteins on the temperature of both normal and sensitized animals. With lambs' serum intravenously administered to normal guinea-pigs he obtained the following results:

5.0 c.c. equals fatal dose.
0.5 c.c. equals limit for fall in temperature.
0.01 c.c. equals upper constant.
0.005 c.c. equals fever plane.
0.001 c.c. equals lower constant.

[13] Berl. klin. Woch., 1910, No. 42.

In sensitized guinea-pigs the above figures were changed to the following:

0.005 c.c. equals fatal dose.
0.0005 c.c. equals limit for fall.
0.00001 c.c. equals upper constant.
0.000005 c.c. equals limit for fever.
0.000001 c.c. equals lower constant.

In 1911, Schittenhelm, Weichardt, and Hartmann[14] experimented upon the effect of the parenteral administration of diverse proteins on animal temperature and came to the following conclusion, which in my opinion, is well stated: "In severe experimental anaphylaxis there is a fall in temperature; in the lighter manifestations there is fever." We regard this as a confirmation of our conclusion reached some years earlier. "Small, especially repeated, doses of the protein poison cause fever, while large doses depress the temperature."

Some years ago Friedmann and Isaak[15] showed that after the parenteral introduction of foreign proteins the increase in nitrogen elimination is greater than can be accounted for by the protein injected. This has been confirmed by the work of Schittenhelm and Weichardt[16] and as has been stated, we found the same in protein fever. Our explanation for the marked increase in nitrogen elimination has been given.

In intermittent and remittent fevers and in relapses in all infectious diseases the phenomena of protein sensitization are fully demonstrated. In the different forms of malaria, chill and fever correspond to the discharge of foreign protein into the blood, just as promptly as anaphylactic symptoms follow the injection of the homologous protein in a sensitized animal. The moment the blood cells rupture and the protozoal protein is disseminated the sensitized cells discharge the lytic ferment by which the foreign protein is disrupted and destroyed, but in this process the poison is liberated.

Local sensitization is frequently established in the mucous membrane of the air passages and of the alimentary canal, also in the skin for two reasons. In the first place, foreign proteins are frequently brought into direct contact with these tissues, and in the second place, foreign proteins introduced into the blood are frequently deposited in the skin and in the walls of the alimentary canal. These local sensitizations characterize many of the infectious diseases. The work of Dunbar and Weichardt on hay fever is a nice illustration. These investigators injected each other subcutaneously with minute quantities of pollen suspension. Immediately Dunbar, being a hay-fever subject, became dizzy and within a few minutes began to sneeze, then a whooping-like

[14] Zeitsch. f. exp. Path. u. Ther., 1911.
[15] Ibid., 1905, 1906, and 1908.
[16] Zentral. f. d. ges. Physiol. u. Pathol. d. Stoffwechsel, 1910.

cough began. The eyes were congested, and an abundant secretion flowed from the nose. The face became swollen and cyanotic, and soon the body was covered with an urticarial rash. After twenty-four hours these symptoms subsided. Weichardt, not being a hay-fever subject, was not affected. That this and kindred affections are not benefited by antisera was abundantly and positively demonstrated by the failure of the so-called hay-fever serum, which was found in no instance to be of special value, and in some it greatly intensified the symptoms.

Our common colds, are instances of local sensitization. Schittenhelm and Weichardt tell of a man who was so deeply sensitized by the inhalation of Witte's pepton that he could tell on entering the laboratory whether the pepton flask was open or closed, and some moist pepton painted on the skin caused the area covered to become red. The high degree of susceptibility to odors from the horse shown by some people has already been referred to. It seems in some instances that this susceptibility is transmitted from mother to child.

A volume might be filled with citations of cases of food and medicine idiosyncracies. That these are, in large part at least, instances of protein sensitization has been demonstrated by rendering animals susceptible to the same food or medicine by injecting them with the serum of the susceptible individual. In other words, passive anaphylaxis has been established in the animal. In this way Bruck has sensitized animals to iodoform and antipyrin with the sera of persons especially susceptible to these agents.

We are compelled to change our ideas concerning the causation of the lesions of the infectious diseases. Formerly we believed the structural changes to be due wholly to the living, growing, feeding microörganisms. For instance, we were sure that the intestinal ulcerations of typhoid fever are caused by the living bacilli. Now we know that these lesions follow the intravenous injection of dead proteins. As has been stated, each foreign protein has its predilection tissue in which it is largely deposited, whose cells it especially sensitizes, and where it is disrupted. This explains the characteristic lesions and symptoms of the different infectious diseases. As I stated in the Shattuck Lecture of 1906: "Bacterial inflammation is essentially a chemical process, or is due to the disruption of cell molecules through the chemical affinity between certain groups in the bacterial cell and certain groups in the cell of the animal. So long as the bacterial cells are alive the chemism that holds the living molecule together tends to resist this process of disintegration. . . . The pathogenic bacterium assimilates the nutritious constituents of the fluids of the animal body, builds them into its own tissue, converts them into substances foreign to the host and, finally, when the bacterial cell goes to pieces either from spontaneous dissolution, or through the aggressive action of

some animal cell, these reconstructed chemical groups are set free and poison the animal, inducing lesions in various tissues, and, in many instances, so interrupting the vital functions as to cause death." It is in harmony with these statements that Friedberger has been able to induce aseptic pneumonia by spraying horse serum into the lungs of guinea-pigs sensitized with the same, and Schittenhelm and Weichardt have established "enteritis anaphylactica" by the reinjection of egg-white into sensitized dogs. It is more than probable that cholera infantum and the kindred summer diarrheas result from the absorption of undigested milk and consequent sensitization. The designation "protein diseases" might be used to cover the majority of bacterial and protozoal diseases, and many of these hitherto regarded as autogenous.

Conclusion. In conclusion, I wish to state that all the problems of protein sensitization have not been solved. It seems to be a physiological law that the specific ferments elaborated by living cells are determined by the proteins brought into contact with them, but as yet we know but little concerning these bodies which we call ferments. That they are labile chemical bodies resulting from intramolecular rearrangement in the protein molecules of the cell seems a plausible theory, but at present it is only a theory. We know but little of the action of these so-called ferments upon their homologous proteins. Our knowledge of the chemistry of protein sensitizers is exceedingly limited, and as I have pointed out, it is highly desirable that work in this direction should be prosecuted with vigor, because we need sensitizers free from the poisonous group. Furthermore, there is the question, why small doses of protein induce fever while large doses have no such effect. At present we have no satisfactory answer to this question. If it could be conclusively demonstrated that the toxins are ferments, the subject of the etiology of disease would be greatly simplified. I have elsewhere[17] given my reasons for holding that the toxins are ferments, and in closing this paper I wish to formulate what I believe to be two biological laws:

1. When the body cells find themselves in contact with, or permeated by, foreign proteins they tend to elaborate specific ferments which digest and destroy the foreign proteins.

2. When body cells are attacked by destructive ferments they tend to elaborate antiferments the function of which is to neutralize the ferments and thus protect the cells.

[17] Trans. Assoc. Amer. Physicians, 1911.

CHRONIC PURPURA, AND ITS TREATMENT WITH ANIMAL SERUM.

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The object of the writers in presenting this article to the profession is to call attention to chronic purpura, place on record the histories of two cases of the disease, and report the results of the treatment of this comparatively rare and protean disease with animal serum.

Discouraged by his repeated failure to influence the disease by the ordinary forms of treatment of purpura as originally summarized by Davis King, Jr., in his Fisk Prize Essay (1836), and modified during recent years, the writer was ready to welcome the facts to which Weil[1] called attention in connection with the use of animal serum in the treatment of purpura, and was pleased to coöperate with his coworker in this article (Meader) in the application of the remedy by the latter to the treatment of the cases included in this article, and to other forms of purpura and hemorrhagic disease less chronic than those herein reported.

Weil's work brought out these facts: that the blood serum of horses, rabbits, and beef creatures, as well as human serum, had the power of controlling hemorrhagic processes by increasing the coagulability of the blood; that beef serum was too toxic for ordinary use; that the serum used should be less than two weeks old; that a dose of 15 c.c. intravenously or of 30 c.c. subcutaneously would obtain results in most cases; that the use of serum locally at the point of hemorrhage favored clotting; that the increased coagulability of the blood persisted for a period of from fifteen days to several weeks after injection.

Case I.—Mrs. H. W. J.; first seen December 24, 1905; aged forty-five years; family history excellent, without taint; great resistance; no specific history. Patient is a woman of splendid education and refinement, who has always lived a temperate and exemplary life, devoting much of her time to study and painting. She has no living children; nine years ago had a miscarriage. Soon after this it was found that she had a uterine fibroid and ovarian cysts, for which a complete hysterectomy was successfully performed. Otherwise she had always been well. Much of her time was spent in the open air, during the summer months on the coast of Maine. When I saw the patient in 1905 she had a severe left

[1] P. Emile, L'Hemophilie, etc., Press Médical, October 18, 1905.

brachial neuritis, was anemic, reduced in flesh, and excessively nervous, but without discoverable physical signs of cardiac or other disease. The neuritis yielded to tonic treatment and high frequency. Within one year after the cure of the brachial neuritis she had an acute suppurative disease of the antrum of Highmore, which was relieved by the usual surgical treatment, but required continuous drainage for three years. The drainage tube was in the antrum when the patient consulted me January 17, 1908. I found her suffering greatly from pains, rheumatic in character, in both legs; joints painful, but no swellings noticeable. She had large varicosities, and considerable infiltration of the skin in spots over the shins, the characteristic and usual accompaniment of long-continued venous stasis. Under rest, tonic treatment, and well-fitting stocking support there was decided improvement of symptoms referable to the extremities until April 11, 1908, when I found her with fully developed purpura rheumatica; both legs were involved; purpuric lesions numerous, more on the left than on the right leg; some of the spots were as large as a silver dollar. Some of the purpuric macules were ecchymotic, others bright red. There were macules on the arms, on the abdomen, and a few on the face. The patient volunteered the information that possibly her condition might have been aggravated by the inhalation of sewer gas. Thorough physical examination failed to show heart murmurs, there was more or less malaise; pulse was small but regular, 88; arteries normal. Systolic blood pressure 110, diastolic 75; pulse pressure, 35. The examination of the urine at this time gave negative results; no abnormalities in the proportion of its solid constituents were found. Blood examination showed a slight polycythemia: reds, 6,200,000; hemoglobin, 100; whites, 12,000. Blood platelets unfortunately were not counted at this time. Stained smear showed but little variation in size; a few poikilocytes. A few leukocytes resembling myelocytes were seen. Polymorphonuclears, 84 per cent.; lymphocytes, 14 per cent.; eosinophiles, 2 per cent. Time of coagulation of blood was normal. Blood cultures have always been negative. In a few days (April 21) a purpuric spot, which was about the size of a nickel on the plantar surface of the right foot, became exquisitely tender and so painful that the patient was kept awake by it; there was a great deal of pain in the right foot, which was swollen, and in the course of three days the tender spot on the sole showed positive evidences of localized gangrene, corresponding in size with the original area of purpura. In due time the necrobiotic patch showed a distinct line of demarcation, and by April 29 the superficial slough had lifted itself; the odor was characteristic of dead tissue. On that day the following note was made: "Patient has new purpuric spots on left ankle. Has swelling of the small joints of both hands, but is without fever."

These rheumatic symptoms continued during several days; finally the hands became purpuric and the pains were relieved. Aspirin seemed to relieve the pains. Gave aromatic sulphuric acid with quinine, nutritious diet, fruit acids, abundant salt, without in any way controlling the purpuric symptoms.

May 8. "Some improvement; a few purpuric spots are fading. On the sole of the right foot there is a new patch of superficial death of the purpuric macule, larger than the first, almost the size of a fifty-cent piece. There are a few erythematous spots over the knuckles of both hands. No fever. Pulse, 78."

May 11. "No new symptoms. The spots on the sole of the right foot emits the usual odor of infarct and final superficial gangrene. There are petechiæ here and there over the entire body, face and arms included."

May 26. "New purpuric spots and joint symptoms follow wherever the patient scratches or strikes herself, or where undue pressure is exerted. In some of these gangrene follows. Discontinued the acid and substituted calcium lactate and phosphomuriate of iron and quinine with the same diet. Never yet have I found the patient with fever."

June 1. "No new spots today unless she pricks herself, then the tendency to superficial breakdown continues."

June 2. "New crop of purpura over legs, ankles dotted, and on the face. 'Hemorrhagic lines' are noted on the abdomen a few following skin irritation or scratching. There are (June 10) a number of erythematous patches around the larger joints of the body."

June 13. Patient was placed in charge of Dr. John Van Duyn, who continued to treat her until my return from abroad on September 19, 1908, when the following note was made: "There has been but slight improvement; the hollows of both feet are healed; the purpura is general; has a troublesome erythema and intertrigo, with eczema in axillæ, groins, and other folds of the body. Ankles are swollen; the purpuric spots on the lower extremities particularly near the ankle are large and of a deep purple color." During the following six months the skin irritation bacame general and made the patient very wretched. There was scarcely a time when with more or less eczema and intertrigo there was an absence of fully developed Werlhof symptoms, including tenderness of the gums, and some bleeding from these on slight cause. There was no hemorrhage from the internal organs. There was, however, an occasional nose-bleed. This may have been due to the crusting and ulceration of the mucosa. On one occasion a purpuric spot on the right side of the nose sloughed. It would be useless to present the full history of this case during the almost three years following, as it would be a repetition of all that has been given. It can be easily understood from the following short abstract:

Patient continued to present some of the lesions originally present almost continuously; there never was a time when she did not show purpuric spots on both extremities; at times there was an addition during several days of purpura rheumatica. The intertrigo was finally controlled and has never recurred. There have been varying periods of spongy gums, with some bleeding. Until we commenced the use of the animal serum, preceded by the vaccine to be mentioned later, the patches of local death, particularly on the plantar surfaces of both feet and around the finger nails, continued exceedingly annoying, and recurred at short intervals. During the past four years the patient has been treated for purpura; the urine has continued normal, save at times when there has been slight bladder irritation, then a faint trace of albumin has been found, and on one occasion there was albuminuria for several days after the injection of the serum. There have been times when either because of the visceral symptoms due to the disease, oftener to the medication, there have been painful gastro-intestinal disturbances. It was found during the second year of treatment that there was but one drug combination which influenced the symptoms in any way, and this proved to be the elixir of the four chlorides, which in turn, when taken during a long period, caused griping and diarrhea. The effect was so beneficial in the general improvement and in the partial control of hemorrhagic symptoms that the patient of her own volition continued the remedy until forced to discontinue for short periods, when she again returned to its use. The bichloride of mercury alone or arsenic alone had no influence on the course of the disease. The iodides invariably aggravated the symptoms. It can be easily understood that during these years many remedies were tried and many suggestions followed. Urotropin among these was without effect.

If we were to summarize this case from early 1908 until January 13, 1911, when we found a small pustule on the right leg of this patient from which a vaccine was made, we would present the characteristic picture of chronic purpura without intermission, never a time when the patient was free from some of the lesions of the disease, with repeated circumscribed gangrenous patches following purpuric macules. At no time were the symptoms of the disease limited to one type of purpura; the lesions were indiscriminately distributed, a mixture of all types, corresponding, however, more closely to the continuous type of chronic purpura described by Bensaud and Rivet.[2]

On January 13, 1911, the authors saw the patient together for the purpose of considering the advisability of giving a normal animal serum or a vaccine which might be elaborated. A small purpuric spot was found covered by a pustule about the size of

[2] Archiv. Générale de Médecine, December 1, 1905

a split pea; from this a pure culture of Staphylococcus aureus was made, which gave a vaccine. The patient received three injections respectively: 50,000,000, 100,000,000, 250,000,000 of the vaccine January 16, 20, and 24. By January 20 the general condition was not disturbed by the vaccine; new purpuric spots continued to appear, but the necrobiosis was favorably influenced by the vaccine.

January 27. 17 c.c. horse serum were injected into the left abdominal wall. This was followed by severe pain, which subsided in several hours.

January 31. The surface looks less blotchy; until today there have been no fresh petechiæ; a few spots were noticed on the fingers about the knuckles; these were erythematous, not hemorrhagic. Urine was slightly albuminous; no casts.

February 6. Today an injection of 10 c.c. horse serum was given, promptly followed by general erythema, which covered the entire body, and tender and painful joints, such as are met after the injection of antidiphtheritic serum.

February 7. Joint pains severe; general erythema multiforme persists. Temperature, 98°; pulse, 78; respirations, 19. There is but one fresh petechia on the patient, and that on the left knee.

From February 6 to 16 inclusive the serum sickness persisted, and included besides the erythema, severe headache, which finally yielded to quinine and sodium salicylate.

From February 16 until March 20 there was decided improvement in all the subjective and objective symptoms. The patient was able to be about, there were no fresh petechiæ, the ecchymotic spots of the old lesions were fading, the joints were normal and in every way the condition was better than it had been in almost three years.

During March and April and until May 15 the patient made material progress, was exhilarated, seemed to be "living in a new world," was happy, and encouraged. She required no medical attention, because the symptoms were held in abeyance, and there were only occasional small cutaneous lesions.

May 15. If patient tires after exertion she notices a few fresh "spots." She walks well. Today there are a number of hemorrhagic macules on both lower extremities over the left knee. In spite of the severe serum sickness which she had after the last injection its effect appears to her so beneficial that she literally "begged for it" today. *Since the use of the vaccine and the serum the antrum has closed.* Barring a recent slight hemorrhagic gingivitis there are no symptoms referable to the buccal or nasopharyngeal mucosæ. There has been no tissue loss about the fingers (hemorrhagic panaritium) since the use of the vaccine or serum.

May 20. Today 12 c.c. of rabbit serum were injected, this was followed by only slight local reaction, no fever. Pulse normal. Within two days two egg-sized nodes formed on the back of the left hand just below the wrist. These were not hemorrhagic, but slightly erythematous. The rheumatic symptoms of serum sickness followed. Her joints were so stiff that the patient could not walk. A peculiar accompaniment of the serum sickness in this case was the invariable stiffness of the neck muscles, anterior and posterior, with tenderness of the included muscles and hoarseness.

June 5. "Patient is now receiving the benefit of the last injection. The puffiness has all disappeared; there is no recurrence in the skin; old petechiæ are fading. The patient thinks the rabbit serum caused more stiffness and pain in the neck muscles than did the horse serum. She feels the same tonic effect which followed the previous injection after relief from the disagreeable erythema and joint symptoms (serum sickness)."

June 13. 5 c.c. rabbit serum injected without untoward symptoms following.

June 23. The patient is positive the last injection given June 13 has been productive of greater improvement than any of those preceding. There have been no new lesions since June 9.

From the time of the first injection, January 27, 1911, until October 6, 1911, eleven injections were given, all of which were of normal rabbit serum except the first two.

Besides the four above reported the following doses were given:

June 25, gave 7 c.c. rabbit serum.

July 12, gave 10 c.c. rabbit serum.

August 19, gave 5 c.c. rabbit serum.

September 6, gave 4 c.c. rabbit serum.

Two more injections, close together, were given between September 30 and October 6.

September 30. "Patient's general condition has improved materially and she has gained flesh, now weighs 136 pounds against 115. Has been able to go to Canada for a change, and during her stay there until the end of the month the purpuric symptoms gave her but little trouble."

The injection given October 6 was into the left arm, and was followed immediately by edema of the entire extremity, with the formation of enormous bullæ. Some of these were as large as an egg, tense, and filled with clear serum. There was no other reaction. The swelling extended to the axilla and the glands were enlarged. The bullæ were opened. In twenty-four to thirty-six hours the swelling subsided considerably, and the general condition of the patient improved.

October 13. Wherever there was a bleb there is a distinct hemorrhagic spot, deep red, nummular, corresponding in size with

the original bulla. Now there is no swelling of the arm, and the patient is thoroughly satisfied with the result of the treatment in spite of the annoying complication.

During the last year we have found that the injections of animal serum in this, as in cases reported by others, are better borne when given at short intervals within from ten to fifteen days, and we have therefore in our treatment of this case "bunched the injections" to the satisfaction of both the patient and the attendants, without serum sickness or symptoms due to anaphylaxis. Since October 11 the patient has received eight injections as follows:

October 14. Gave 2 c.c. fresh rabbit serum.

November 11. Gave 1½ c.c. fresh rabbit serum.

December 16. Gave 1 c.c. rabbit serum.

February 10, 1912. Gave 0.6 c.c. fresh rabbit serum.

June 21. Gave 1 c.c. fresh rabbit serum.

June 28. Gave 1 c.c. fresh rabbit serum.

July 6. Gave 1¼ c.c. fresh rabbit serum.

July 13. Gave 1 c.c. fresh rabbit serum.

July 31. Made a blood count: White blood corpuscles, 7400; red blood corpuscles, 3,552,000; platelets, 1,136,000. The latter figure is about three times more than normal. We also find that the smaller doses given at short intervals control symptoms and have the tonic effect just as do the larger doses, without untoward complications.

In this case it may be said the animal serum has been given a long and fair trial. We are thoroughly convinced that its effect has been purely symptomatic and not curative. We are further convinced that besides its effect in controlling the hemorrhagic lesions between the injections the serum has had a decided tonic and exhilarating effect. We wish to emphasize the fact that this woman at the present time is still suffering from chronic purpura; that the pathogenesis of this as other cases is clouded; that there is an underlying constitutional disturbance, in all probability, which we have not unearthed; but the patient as well as her attendants realize the fact that we have at present no remedy which controls her symptoms so well as does the injection of the animal serum. As before, the slightest traumatism causes subcutaneous hemorrhage, which is likely to lead to superficial death of the included skin. There has been but a single physical sign added to those already given. During the months of June and July, 1912, in spite of a good general condition, the area of splenic dulness materially increased, and the organ itself was easily palpable below the free border of the ribs. The coagulation time of the blood has continued normal; the blood clot resulting has remained non-contractible; all these conditions are characteristic of the chronic types of the disease. The blood platelets have shown material increase.

October 18. Patient spent a confortable summer on the coast of Maine; is without annoying symptoms; there are only occasional light colored purpuric spots, usually over the knees, symmetrical; and the spleen is no longer palpable.

Case II.—Mrs. H. G. L., of Auburn, N. Y. Consultation with Dr. Woodruff June 27, 1911. Aged fifty-six years. Mother of two children; always feeble; fearful of cool air; always had a capricious appetite; "unable to eat as others do;" during entire life has been exceedingly hypersensitive. Passed the menopause at the age of forty-nine years without incident. Patient is an intelligent, nervous, well-developed woman. Family history clean, without taint, no suspicion of hemophilia or specific disease.

Previous History: Shortly before Dr. Woodruff first saw the patient, six years ago, she had practically starved herself; was feeble, and thought she needed "rectal treatment," which she finally received from three sources. One operator did "an extensive rectal operation," probably excision of a hemorrhoid and stretching of the sphincter; the second was called who "did something which made matters worse;" finally the patient found her way to Philadelphia, where she was successfully treated, and so far as her rectum is concerned she made a satisfactory recovery. For five years the patient has noticed "black and blue spots" on her body; they gave her no discomfort, coming and going, and were considered of no importance. Beginning with January, 1911, these were associated with marked symptoms of purpura, many of the earmarks of scorbutus, some of the larger hemorrhagic type. At times there was an admixture of purpura rheumatica, when she had severe pains in her legs and joints, with petechiæ covering the extremities and spots also on trunk, neck, and face, particularly about the eyelids, external canthi, and over malar bones. Toward the end of January, 1911, she commenced to show marked evidences of gingival purpura. The entire mucosa about the teeth became involved. This was spongy and purple; over and between each tooth when I first saw her the membrane was so swollen that "purple bags," as the intelligent nurse expressed it, "hung down and between the teeth." These looked like individual large blue grapes; made the patient uncomfortable, because of their size and tenderness; were so spongy and succulent they bled on the slightest touch. The nurse made the following note: "These swellings gradually extended around the whole mouth, looking like purple bags over each tooth. These were more tense just before they bled freely, after which the swelling subsided, but only temporarily." Ankles were swollen and tender.

For years the patient's digestion has been impaired. She feared to take food, as she could bear but little, and after several examinations of her stomach contents was told she was suffering from hyperacidity. Besides the gingival purpura at the time of my first

visit we found purpuric spots over her lower extremities; there were also "black and blue spots," which varied in size from a twenty-five-cent piece to macules which could scarcely be covered by the palm of the hand. These were tender and contained small palpable nodules of coagulated blood. Besides these large macules there were characteristic petechiæ, bright red pin-point to split-pea-size over the trunk and extremities, while here and there were remnants of former hemorrhages in pigment deposits. The patient had had severe epistaxis at varying intervals. At the time of our first consultation all of the cutaneous and gingival symptoms were at their height; the teeth could not be properly treated because of the tenderness of the gums. The stomach was intolerant and irritable, and the patient was unable to take sufficient nourishment, and had refused necessary food. She was obstinately constipated, and volunteered the information that she could never eat salt. She slept poorly.

Blood count: White blood corpuscles, 3800; red blood corpuscles, 4,700,000.

Differential count: Polymorphonuclears 71 per cent.; large mononuclears, 25 per cent.; small mononuclears, 4 per cent.

The coagulation time of the blood appeared to be normal, and there was no contraction of the coagulum. The arteries showed evidences of arteriosclerosis; the radial and popliteal arteries were abnormally tense and evenly thickened. The pulse in the dorsal pedal artery (left foot) was indistinctly felt. The area of cardiac dulness was slightly increased to the left; the impulse was heaving; there was a slight hemisystolic aortic murmur; the second aortic sound was accented; the mitral sounds were muffled; there was no distinct murmur in the mitral area. The area of liver dulness was slightly increased below the free border of the ribs. Systolic blood pressure, 160 mm. Hg.; diastolic pressure, 120 mm. Hg.; pulse pressure, 40. Repeated urinary analyses showed nothing abnormal, save that occasionally the specific gravity dropped to 1010, when the solid constituents were correspondingly lowered. Range of temperature, from 99° to 101°; pulse, 96; respirations, 20. Deep and superficial reflexes were all normal except the patella tendon reflexes, which were markedly exaggerated. The pains became so severe before the consultation that sedatives were needed "for comfort even during the daytime." She was bedridden at this time. After our consultation it was decided to insist on a rational diet, in spite of all objections and previous experiences, and to inject animal serum.

June 29. Injected 7 c.c. fresh rabbit serum (Meader) into the left mesogastric region. We quote from the nurse's report: "The night after the injection there was a slight redness around the spot of injection. The next morning the same surface was slightly mottled. The muscles were sore on that side of the patient's

abdomen, which she decided was the nervousness of changed conditions. *The pains in the legs ceased, so that she never after needed sedatives except two grains of veronal at bedtime; nothing during the day.* The purple spots began to fade and no new ones appeared except just under the left knee. Mrs. L. has become much interested in her case, and is trying to eat more, and now goes out-of-doors longer each day."

July 8. The patient has improved materially; is looking well, and eating better than before; ankles are neither swollen nor painful; there are only a few petechiæ; no new patches; gums are decidedly improved; do not bleed; are retracting; mucosa looks healthy. Injected 14 c.c. fresh rabbit serum today (Meader).

The nurse gave the following report: "The second treatment (injection) was given Saturday afternoon, July 8. In two hours Mrs. L. began to have 'nervous chills' in left hip and extending down the leg. The point of injection was sore at once. Patient slept well during the night following. The next day there was a red spot about the size of the palm of the hand around the injected spot, which itched considerably. This spot extended over the entire abdomen to the pubis. Temperature, 100°; pulse not materially disturbed. Flesh was hot and dry; felt unconfortable; had severe headache and aching joints. Used lead and opium wash locally. At 9 P.M. began to perspire; pain ceased; temperature fell to normal, and patient slept well. For several days there was considerable dizziness when the head was moved. The skin and gum condition continued to improve, and the quantity or urine was increased to 2100 c.c.; some days, 2700 c.c. Patient helped herself better and was happier and encouraged."

July 18. "The purpuric symptoms are held in abeyance; improvement is continuous; suffers but little from gingivitis; the spongy condition of the gums has practically disappeared; no epistaxis; has no pains. Is eating well and takes a reasonable amount of nourishment. Temperature, 98°; pulse, 78; systolic blood pressure, 130. Urine free and normal."

July 24. Patient was found materially improved, and is looking much better. Gums retracted and look healthier. A few remnants of petechiæ left in the pigment deposit, and black and blue areas. On external surface of left ankle there is a long black and blue area. Feet are warm. Pulse in dorsal pedal artery distinctly felt. At 4.30 P.M. 17 c.c. rabbit serum injected (Meader).

It was after this injection that we had evidences of alarming anaphylaxis. Almost immediately after the injection the patient became drowsy. At 6 P.M. had a chill which lasted until almost 11.30 P.M. Considerable nausea. Had a desire to defecate (unsuccessful), and patient fainted and became cyanotic. Was returned to bed. Dr. Woodruff found her with weak pulse. She finally vomited a little. There was a continuous desire to go to stool. All these symptoms

correspond with those found in animals who are injected at long intervals, and are attributable to increased sensibility of the individual to the serum. Patient recovered fully in a few days from the effect of the injection, and the improvement in all symptoms was phenomenal.

August 14. Except a small ecchymotic spot on the plantar surface of the left foot and slight sponginess of the gums over the right upper canine there are no remnants of purpura.

October 4. Received 2 c.c. rabbit serum because of petechiæ on the legs. The gums are normal.

Blood count: Red blood corpuscles, 4,028,000; white blood corpuscles, 3600.

Differential count: Polymorphonuclears, 57 per cent.; small mononuclears, 29 per cent.; large monoclears, 14 per cent.

No untoward symptoms followed this injection. Since November, 1911, there have been no evidences of a recurrence of chronic purpura.

Patient was thoroughly examined August 1, 1912, when the following note was made: "Has recovered completely from her chronic purpura, and has been without recurrence since last seen. She has normal mucous membranes; has gained in weight; color good; blood state good. Blood pressure, 140; respirations, 18; pulse, 76. Arteries slightly tense. Urine normal. Bowels constipated. For three or four weeks has had recurrence of burning sensation and points of tenderness in stomach region which she had many years ago. The burning is exceedingly annoying, and the nervous system is hypersensitive. The neurasthenic element is still in the ascendency. Tongue clean."

Stomach analysis: Amount 50 c.c.; free hydrochloric acid, 40 per cent.; total acidity, 79 per cent.; lactic acid, very slight; blood, very slight; butyric acid, present; red blood corpuscles, few.

Microscopic examination: Starch granules; squamous epithelia. Her disagreeable stomach symptoms were controlled by belladonna and orthoform, with alkalies, and she is now (October 18, 1912) enjoying comparatively good health.

In the light of our recent experiences with these cases, and the knowledge gained by the study of the literature on the subject and animal experimentation, we would suggest in the future, to prevent annoying anaphylaxis, that similar cases be treated with injections of the serum during ten-day periods, the number of the injections to be given and the dosage to depend on a thorough study of the effect of a safe initial and second dose. The number of cycles of treatment should depend on the tendency of the individual case to relapse. Our second case, so far as evident symptoms of chronic purpura are concerned, in spite of its former chronicity during a period of six years, seems to be cured. It is unnecessary

to give the large doses which are suggested by some authors, one having given as high as 250 c.c. of fresh animal serum.[3] In both of our cases the general improvement of the patients and increased weight almost immediately following treatment were satisfactory. Trembur[4] has had similar experiences. The mental condition in both of our cases was improved. Case I expressed herself as follows: "The first and second days one aches all over and feels seasick; joints ache, and you feel just ugly and weak. There is a continuous desire to go to stool. After the fifth day you feel as if you had been given a great big tonic. The injection has an enormous effect on your mental state; it lifts you, and makes you feel better in all respects."

In "sporadic" hemophilia and acute purpura the results with animal serum are permanent, and we have had definite cures. In chronic purpura the prognosis, so far as permanent cure is concerned, is less favorable. The serum controls the symptoms in most cases, but it may be assumed from our present knowledge that the injections must be repeated. The serum of the bovidia is not recommended, because of the violent reactions which may follow its injection, including fever, rigors, cyanosis, and vomiting. Rabbit serum is recommended for all forms of hemorrhagic conditions requiring serum treatment; it is easily obtained by means of aseptic bleeding, and contains all the elements which are needed to control "dyscrasic hemorrhages." If necessary in an emergency, antidiphtheritic serum may be substituted until a fresh serum can be obtained. Recurring purpura with pernicious anemia is favorably influenced by the injections of animal serum, but in these cases there is always a strong tendency toward relapse. With chronic purpura and purpuric symptoms due to hereditary hemophilia the results from animal serum are at best temporary; repeated injections are necessary to control the hemorrhages and the massive types of visceral hemorrhages are controlled imperfectly. The greatest value of the treatment in these cases, according to Weil,[5] is in the prophylactic injections of the serum before operative procedures are instituted. The results of treatment with animal serum are better in the type of hemophilia which Weil has characterized as "sporadic" or "accidental," in contradiction to the hereditary disease, a condition met in advanced life, accidentally encountered in normal individuals of both sexes. In these cases the blood reacts favorably to normal blood serum, and is thereby robbed of its hemophilic tendencies. The coagulability of the blood in these cases is favorably influenced by the serum, in the average cases

[3] Pigot, Gaz. Hebd. de Med., October 17, 1897.

[4] Serum Behandlung bei Hemophilie, Mitteilungen aus den Grenzgebieten der Med. u. Chir., 1911, vol. xxii, p. 93.

[5] L'Hemophilie, etc., Presse Médicale, October 18, 1905. Tribune Médicale. Paris, January 12 1907.

during three or four weeks. If such subjects demand surgical interference the most favorable time for operation is forty-eight hours after the injection. In chronic purpurics and hemophilics the serum may be given intravenously if such method of introduction is selected, with perfect safety, and without increase of hemorrhage, for the puncture of the vein in these subjects is promptly closed by its own elasticity, as has been repeatedly demonstrated by Weil.

The literature bearing on chronic purpura is meager and unsatisfactory, the classification of the purpuras offered by the French and German schools are also unsatisfactory; while our knowledge of the pathogenesis of many forms of purpura rests on an insecure and poorly constructed foundation. The cautious and continuous study of all types of chronic purpura makes positive the fact that the clinical picture is kaleidoscopic, and the cycles of the disease include repeated recurrences of all classified types of the disease in the individual case. In the chronic cases, with a simple purpura, there may be a prompt addition of the rheumatic form, and while this seems in the ascendency, the hemorrhagic nature of the disease may be emphasized by drains from one or more mucous surfaces, occasionally hemorrhage into the brain or into hollow or solid viscera. Besides this our experiences justify the conclusion that chronic purpura may at times alternate with erythema multiforme, and included visceral symptoms, while in occasional cases, at times during their course, two or more types of purpura may be present and persist with varying intensity during limited periods at the same time.

In rare cases (one of which we have reported), whether because of embolic infarct, thrombosis, or necrobiosis, due to some other unknown pathologic cause, death of the infiltrated tissue results, corresponding with one or more of the original purpuric spots, all this in the presence of multiform hemorrhagic lesions, cutaneous, articular, and visceral. Immerman[6] was in all probability correct when he contended that (1) simple purpura, (2) purpura rheumatica, Schoenlein's disease, (3) Henoch's purpura, involving skin, joints, and gastro-intestinal mucous membranes, and (4) purpura hæmorrhagica, or morbus maculosis Werlhof, are all identical, simply differing from each other in degree and intensity of constitutional symptoms. Chronic types of purpura may include, besides the hemorrhagic lesions, erythema, urticaria, and occasionally angioneurotic edema (Quincke's disease).

The histories of the cases of chronic purpura which have fallen under our observation prove them to be rebellious to ordinary treatment, and when influenced by treatment the periods of improvement by the older methods and drugs are exceedingly short,

[6] Ziemssen's Cyclopedia.

for repeated relapse is likely to be the fate of all suffering from the disease. Thus one of the writers (Elsner) has seen cases covering a period of twelve and fourteen years respectively. Osler mentions a case which continued thirty-six years, and Halstead operated on a case of cancerous disease in which the patient had been purpuric since childhood.

Probably the most complete *resume* of our knowledge of chronic purpura with included histories of cases is from the pen of Bensaud and Rivet.[7] These authors concluded that there is little mention in literature of the subject outside the common form known as Werlhof's disease. There are included references to articles mentioning 4 cases of the chronic form. These are (1) Rade, 1844, the case of a man, aged thirty years, who had two attacks in eight months; (2) Lancereaux, 1861, a chronic case, with large nasal and gingival hemorrhages, which finally died; (3) Lasegue, 1877, a case which appeared to be cured after three and a half months; (4) Denys, 1877, observed the case of a woman, aged forty years, who had successive attacks during two years. The article of Bensaud and Rivet further includes references to the researches of Hagen (1900), in which he emphasizes that the "chronic form is of certain frequency, and that it shows itself in successive attacks and remains apyretic." He reports several cases, and is more hopeful in his prognosis than our experiences would justify. One of his cases, a youth, aged eighteen years, had repeated attacks of purpura since his ninth year. Another, a woman, aged twenty-two years, had the disease since her seventh year. She had repeated epistaxis, and when aged eighteen years, commenced to have attacks of hemorrhagic purpura with her menstruation. One of his cases died in three months. A man, aged twenty-five years, had been purpuric since his tenth year, and finally had "hæmorrhagic periods," which were apyretic and characteristic of the chronic type of the disease in the multiform and varied lesions of purpura. Bensaud and Rivet further refer to a series of the chronic type in which, as in one of our reported cases, there were "periods of quiescence, during which the return to apparent health seemed complete, but the phenomena recurred on extreme fatigue." Their studies justify the following conclusions: Chronic purpura may present a variety of clinical pictures. There are two principal classes: (1) the continuous form, and (2) the intermittent form.

1. In the continuous form of the disease, patients present symptoms of general debility and rheumatism or of gastric or intestinal troubles. Both of our cases presented the latter. Examination of these patients shows ecchymoses or purpuric spots, which have been present for years, to which no importance has been attached because of their rapid disappearance. Epistaxis and

[7] Archives Générale de Médecine, 1905, I. 24.

gingival hemorrhages are common in these cases. There are almost always some manifestations of purpura either on the skin or mucous membranes or some evidence of the hemorrhagic diathesis which is chronic and continuous, but without the great accidents which characterize the free crises of purpura hæmorrhagica.

2. The intermittent form of chronic purpura. This form appears to be more frequent. In these cases crises are separated by intervals of varying length. In the crises there are "abortive and anomalous phenomena." Crises are sometimes preceded for months or even years by frequent isolated hemorrhages, epistaxes, and stomatorrhagias. By themselves these crises are in no way distinguishable from Werlhof's disease. Contrary to current opinion these may be accompanied by febrile movement. After a variable length of time, often prolonged by the "subintrant attacks" so well known in the course of all purpuras, a latent phase follows when the patient appears cured. Until the appearance of a new crises there are no morbid phenomena. More often, if questioned carefully, however, some symptoms are mentioned; these include epistaxes, ecchymoses following the slightest traumatism or prick or menorrhagia suggesting uterine disease. At other times the general condition is disturbed; patients complain of stiffness; they frequently complain of digestive troubles; digestion is slow, painful, and accompanied by heaviness after meals; patients accommodate themselves to this condition until, as a result of influences not well determined, a new crisis follows, confirming the existence of the *chronic and intermittent* type of the disease. There are many clinical modifications. For instance, in three cases Bensaud and Rivet report a true alternation of mucous or visceral hemorrhagic crises with the purpuric eruption, which disappeared when the large hemorrhages appear, only to reappear quickly after them. A curious fact observed is that an intervening infectious disease (variola in one case, and erysipelas in another) does not assume a hemorrhagic character. In the cases studied by Bensaud and Rivet the duration was extremely variable. The long periods of quiescence in the intermittent form of the disease, and the further fact that most cases of chronic purpura are of this type, and the almost complete disappearance of subjective complaints during the periods are the reasons for the failure of many authors to recognize the existence of chronic purpura. Recurrences for more than twenty years were observed. Intermediary periods may be for a long period, as seven, eight, and in one case seventeen years.

Mode of termination is also variable. On account of the long latent periods it is never justifiable to conclude that the patient is cured. Patients may die during a crisis, so that one cannot call the disease benign. *Hemorrhage is the cardinal symptom of all types of chronic purpura.*

Diagnosis of chronic purpura is aided by the fact that the ma-

jority of observers are agreed that the blood clot does not contract, that the coagulation time is normal, and there is a belief among some that the blood platelets are diminished. This is not, however, uniformly true. The role which the blood platelets play in these cases and in the acute forms of the disease is now under consideration by the profession; it would seem that their presence in the blood is of great importance in aiding coagulation. This question will be more fully considered in the second part of this article.

The consideration of anaphylaxis in the use of animal serum is of the utmost importance, as the sensitization which may follow after the second injection or at any time during a series of injections may prove to be associated with serious symptoms, including sudden dyspnea, cyanosis, and in animal experimentation death has occurred. Fortunately this condition is rare in man. In both of our cases disagreeable symptoms have approached the more serious symptoms, which have resulted from animal experimentation in guinea-pigs. The method of treating these cases with small injections at short intervals during ten-day periods will in all probability prevent this disagreeable and annoying sequel. Auer, and Lewis and Auer[8] have shown that atropin sulphate is a distinct protection against the asphyxia of immediate or acute anaphylaxis in the guinea-pig. These observations have been confirmed by others.[9] The work of Karsner and Nutt[10] on the relation of the intoxicating dose of Horse Serum to the Protective Dose of Atropin in Anaphylaxis in the Guinea-pig" gives some promise of success in its application to the human subject. At present there can be no objection to the administration of belladonna or atropin in small and safe doses following the second injection of the serum with the hope that a disagreeable and possible serious anaphylaxis may be prevented. Better still is the administration of the serum as suggested at short intervals during a limited period, preferably ten or twelve days, the thorough inquiry into the individual case to learn of possible idiosyncrasy or previous treatment with diphtheritic antitoxin. The consideration of anaphylaxis in connection with the treatment of hemorrhagic disease with animal serum will always claim the earnest attention of the therapeutist.

Serum Sickness. In occasional cases, as in Case I, serum sickness may be annoying but not alarming. It may be associated with urticaria, arthralgia, and myalgia, but is evanescent. In

[8] Acute Anaphylactic Death in Guinea-pigs, Jour. Amer. Med., 1909, liii, 458; The Prophylactic Action of Atropin in Immediate Anaphylaxis of Guinea-pigs, Amer. Jour. Phys., 1910, xxii, 439.

[9] Anderson and Schultz, The Cause of Anaphylaxis and Some Methods of Alleviating It, Proc. Soc. Exper. Biol. and Med., 1910; A. Biedl and R. Kraus, Die Serum Anaphylaxie Beim Meerschweinschen, Wien klin. Wochenschrift, 1910, xxiii, 385.

[10] Section on Pathology and Physiology, American Medical Association, 1911, p. 128.

spite of this disagreeable complication, purpurics are so much improved that they offer no objection to the repeated use of the serum.

THE RATIONALE OF THE SERUM TREATMENT OF HEMORRHAGIC DISEASES. Considerable literature has recently accumulated tending to show that the introduction of a foreign serum into the body of a patient afflicted with a hemorrhagic disease tends to bring about an improvement. The explanation for the phenomenon is at present not clear. However, a statement of facts in the case may be of interest, and perhaps lead to a clearer understanding of the problem involved.

Various explanations have been made as to the cause of hemorrhages, which may be briefly mentioned; abnormal thinness of the bloodvessel walls; abnormally high blood pressure; excessive amount of blood for the capacity of the bloodvessels; an inherited predisposition to a faulty structure of the cells of the body and blood; defects in the mechanism of coagulation, etc. In view of the fact that the coagulation of the blood in many of these patients seems to be delayed, it will be of interest to review the factors involved in coagulation.

There is present in the plasma a protein called fibrinogen. During the process of coagulation this protein is used up so that in blood serum which exudes from a blood clot its presence cannot be detected. The substance which unites with fibrinogen to form fibers of the clot is known as thrombin. It is not present in an active form in the blood plasma, but is formed soon after it escapes from the bloodvessels, and is present in the blood serum or the clot. Its formation is a complicated matter.

According to Howell there are two hypothetical substances existing in the blood plasma—antithrombin and prothrombin. When the latter unites with calcium salts thrombin is formed, but under the usual conditions in the bloodvessels the calcium salts are restrained from uniting with the prothrobin by the antithrombin, so that clotting in the vessels does not normally occur. When, however, blood is shed, thromboplastic substances from blood platelets and injured cells neutralize the antithrombin, so that the calcium salts are free to unite with the prothrombin and thus form thrombin. Thrombin unites with fibrinogen and forms fibrin—the essential part of a clot.

These two substances—fibrinogen and thrombin—are definite bodies. They can be isolated in a pure state and examined by the experimenter. Fibrinogen can be salted out of blood plasma or from the pathologic fluids of the body cavities, such as pleuritic fluid, hydrocele fluid, or ascitic fluid. A watery extract of thrombin may be made by appropriate means from blood serum, and if added to any of these abnormal body fluids above mentioned will bring about the immediate formation of a clot.

The point of special interest to us is the source of the thromboplastic substances above mentioned, which brings about the neutralization of antithrombin. Where do these substances, so-called cytozymes, come from? It was at first stated that they come from the leukocytes, but doubt is thrown on this source because leukoctyes remain intact for a long time after being shed. They may be washed and may perform their normal phagocytic functions in the test-glass long after the clot has formed. More recently attention has been focused on the blood platelets. If the fresh shed blood is observed under the microscope these platelets are seen to agglutinate, and soon delicate fibrils are seen to radiate out from the masses of platelets. Methods have recently been devised for easily and accurately estimating the number of platelets per cubic millimeter of blood. The number for normal blood is placed at 250,000 to 400,000 c.mm.

The count of platelets in various blood diseases is interesting. Wright and Kinnicutt find that in secondary anemia the count is high, while in primary anemia the count is low. Duke finds that it is of value to differentiate coagulation time from bleeding time, that is, the time a wound will continue to bleed. He finds that in cases of prolonged bleeding time the blood-platelet count is low. He reports that a rabbit injected subcutaneously with diphtheria toxin, after a period of two weeks suddenly developed petechiæ and a prolonged bleeding time, which persisted for three days, and then disappeared. This disturbance was associated with a rapid decrease in the platelet content of the blood, and recovery followed their increase. He reports that in such diseases as idiopathic purpura hæmorrhagica, chronic ulcerative colitis, aplastic anemia, nephritis, the number of platelets is reduced, and that recovery is associated with their increase.

The blood platelets Wright believes come from the megakaryocytes of the bone-marrow. It is thought that they are short lived and are reproduced very rapidly, perhaps a sufficient amount to resupply the body can be made in four days. They are not found in defibrinated blood or blood serum.

Starling believes that the so-called blood platelets are not present in the blood plasma, but are substances, possibly precipitates, formed when the plasma touches a foreign surface. The constitution of these bodies or substances is immaterial so far as this discussion is concerned, since Starling attributes to them functions in the phenomenon of coagulation.

Having detailed to some extent the facts known to be associated with coagulation of the blood, let us return to our main problem and inquire farther why foreign and homologous serums appear to cause a patient to improve. It will be at once recognized that transfused blood will contain blood platelets intact, while homologous and foreign sera contain only the fragments or disinte-

gration products of these platelets, which are the real zymoplastic or thromboplastic substances; so that these bodies may be of service immediately in decreasing the bleeding and coagulation time. But, in addition to this, the injection of a serum into the body of an individual stimulates that body to the formation of antibodies.

Precipitins are formed and, further, the body becomes sensitized to this particular kind of serum. Using the nomenclature of von Pirquet, ergin is formed. Ergin is a hypothetical substance in the blood which is manufactured by the body cells for the purpose of digesting or protecting the body from a subsequent dose of the serum. During the process of digestion just mentioned a toxic body is liberated which produces the toxic symptoms.

Now it has been shown by Moss and Brown that the introduction of a foreign serum into a rabbit, whether sensitized or not, does not change permanently the relation between the kinds of leukocytes, but for a brief period after the injection there may be a marked relative increase of polynuclears, with a decrease of lymphocytes. The lymphocytes are manufactured in the lymph nodes, but the polynuclears are known to be made in the bone-marrow, where the megakaryocytes are located. Now may not the question be raised—Is not the physiologic change brought about by the immunization with a serum, an expression of unusual activity in the bone-marrow manifested by a shower of polynuclears and blood platelets, which latter improve the coagulating properties of the blood? In other words, are the blood platelets increased with immunization by a serum? Duke's work with transfusions suggest that they are, but so far as we know the question of increased platelets during immunization with a foreign serum is not answered.

An interesting recent observation in this connection is that of Duke's. He finds that when a large dose of a toxin (benzol or diphtheria toxin) is injected subcutaneously into a suitable animal a strong irritation is produced, and the platelet count decreases; while if small doses are given, a mild irritation is produced and the platelet count increases. In our cases above reported marked improvement followed the subcutaneous injection of small doses of rabbit serum, which may be explained by the supposition that a mild irritation is produced by the toxin liberated by the action of ergin, which irritation may have increased the platelets. This increase in platelets may increase the coagulating property of the blood. We have observed the blood platelets to be very numerous after a series of small doses of serum. This is accompanied by the clinical fact that the patient is much improved.

THE PRESENT VALUE OF THE WASSERMANN REACTION.

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In recent years one of the greatest advances in medicine has been marked by the adoption of the Wassermann reaction in the diagnosis and treatment of syphilis. It has necessitated extensive revision of many of the older conceptions of the disease. The definite relationship of syphilis to the so-called parasyphilitic lesions has been established. Further, it has proved of immense service in the differentiation of doubtful cases, such as ulcers, growths, various bone diseases, etc. Greatest of all, however, its value in the treatment of syphilis has been abundantly demonstrated, as it has provided a method by which the success or failure of therapeutic measures can be determined.

Even at the present time, however, different authorities report considerable variations in the results of this reaction. Its technique is being almost continually modified, and the exact interpretation that can be placed on its application to the diagnosis and treatment of syphilis is not yet sufficiently definite.

Even for normal individuals the results are disputed, an average being from 0.3 to 1.2 per cent. of positive cases, although Noguchi reports as high as 3.6 per cent. These figures, of course, depend on the class of cases examined, as many who eventually show definite syphilitic lesions give no history of the earlier stages of the disease.

In the primary stage of syphilis the number of positive reactions varies in the reports of different authorities from 64 to 92 per cent. It is certain, however, that in most cases a positive reaction can be obtained by the end of the fourth week, so a definite diagnosis can generally be had a week or two before the appearance of the secondary eruption. In about 40 per cent. of cases the Wassermann reaction is positive when the initial sore appears, and the number of positive reactions becomes progressively more frequent until the development of the secondary eruption, at which time over 90 per cent. are positive. The earliest occurrence is reported by Lesser, who found a positive reaction as early as the eighth day after exposure. In this case the initial lesion appeared fourteen days later, and was followed six weeks afterward by a typical roseola. In my experience in about 9 per cent. of cases where no treatment has been received the reaction did not become positive until the first or second week after the development of the secondary eruption. Clinical evidences seem to show that with the development of a positive Wassermann reaction there is general systemic invasion of the syphilitic virus.

Experimentally, it has also been demonstrated by Neisser that with the development of a positive reaction the lymphatic glands and other tissues of the body become capable of transmitting the disease to apes. As a rule therefore there is systemic invasion of the virus some time before the development of the secondary eruption, and in a large percentage even before the development of the initial sore.

In secondary syphilis, positive results are reported from 80 to 100 per cent. Indeed, one may say that practically every untreated case gives a positive reaction in this stage, although its appearance may occasionally be delayed until one or two or even three weeks after the appearance of the secondary eruption.

In the tertiary stage, positive reactions are reported in 60 to 100 per cent. of cases, but more correctly in about 80 per cent. The figures in this stage of the disease, although they vary considerably, depend chiefly on whether the syphilitic process is active or healed. Almost every active tertiary lesion is associated with a positive reaction.

The most constant results are undoubtedly in secondary and hereditary syphilis. In congenital cases almost all give a positive result, even at birth (95 per cent. or over). That this is of practical importance is obvious, as many children after birth develop snuffles, and a positive Wassermann reaction both confirms the diagnosis and indicates that active treatment should be instituted at once. It also assists therefore in clearing up the diagnosis of stillbirth and habitual abortion. In 56 per cent. or more of apparently healthy women, the mothers of syphilitic children, there is a positive reaction. Similarly, the children of syphilitic mothers are not immune to syphilis, but, as can be shown by the Wassermann reaction, are either syphilitic or healthy, or may later become infected. Thus a woman having given birth to a syphilitic child, and having a positive reaction, is to be considered as having latent syphilis, and should be given specific treatment. Also a positive reaction in the child of a syphilitic mother, even though the child looks healthy, indicates that it also ought to be treated.

Pregnant women who have had a previous history of repeated abortions or stillbirths, and who are found to have a positive reaction, should be given antisyphilitic treatment, and in this way healthy children may be born.

In relation to the choice of wet-nurses, the importance of this reaction is obvious.

After the clinical signs of syphilis have disappeared, many cases, although apparently in good health, remain in a latent syphilitic condition. Reports in this phase of syphilis average about 65 per cent. of positive reactions in the early latent stage, and as many as 47 per cent. in the late stages. These figures are naturally subject to the widest variation, as the treatment of syphilis has

been so irregular in efficiency. Even in untreated cases it is difficult to estimate exactly how many will go on to a latent stage, and how long this may last, and whether it will lead to the late manifestations of syphilis, such as aneurysm, tabes, and paresis. By means of the Wassermann reaction the existence of latent syphilis may be recognized and adequate antisphyilitic treatment commenced. In this way the modern methods of treatment, which are guided by serum tests, have very materially lowered the percentage of cases of syphilis which have gone on to a latent stage, and so also of these latent cases which have eventually developed late syphilitic lesions.

In this latent stage of syphilis there may be no clinical manifestations which are obviously syphilitic, yet commonly such cases become extremely anemic, and often are the subjects of certain vague symptoms which usually disappear rapidly under antisyphilitic treatment.

It is not uncommon to find cases, even when treatment has been fairly thorough, where the reaction remains positive for ten or fifteen years after infection, and cases are reported positive after forty years. Undoubtedly many such latent cases become spontaneously cured, yet all are liable to develop further manifestations of syphilis.

Reinfection with syphilis occasionally occurs, particularly in cases which have been satisfactorily treated; but so far as I know in no case presenting at the time a positive reaction. Certainly apes resist the development of syphilis so long as the serum reaction remains positive.

In the late manifestations of syphilis, such as the so-called parasyphilitic lesions, perhaps more than in any other relation, the Wassermann reaction is called on for discriminating diagnostic tests, and is also of special use in indicating the line of treatment which may arrest the progress of the disease. The importance of any reaction which can aid in distinguishing a gumma from other forms of cerebral tumor is undisputed. Thus, as a general rule, no case of operation for cerebral tumor should ever be undertaken without a negative Wassermann reaction, and in all cases of epilepsy starting in adult life this reaction is also suggested.

Tabes and general paresis are not then parasyphilitic, but metasyphilitic or truly syphilitic lesions. This does not mean that all cases of tabes are syphilitic in origin, as undoubtedly ergotism, anemia, pellagra, and a great variety of other conditions are associated with a moderate degree of degeneration of the posterior columns of the spinal cord, and consequently may present some symptoms of ataxia. The fully developed, progressive type of the disease is, however, definitely syphilitic. As a general average in paresis, 81 per cent. in the blood serum and 85 per cent. in the spinal fluid, and in tabes 65 per cent. in the blood serum

and 68 per cent. in the spinal fluid give positive results. In these cases it is the progressive types, with lymphocytosis in the spinal fluid, which furnish the positive reactions, while the stationary cases are generally negative. In cerebrospinal syphilis the reported results are rather conflicting, about 50 per cent. giving positive reactions in the blood serum and from none to 58 per cent. in the spinal fluid. It has been considered as a point of diagnostic importance that relatively few cases of cerebrospinal syphilis give positive reactions in the spinal fluid, yet when larger amounts of this fluid are used for the test, the positive reactions obtained closely follow the results in the blood serum. Cases of cerebrospinal syphilis usually give rather less frequent positive results than are found in tabes. Probably this is because many cases of cerebrospinal syphilis present only the results of the disease and not an actively syphilitic lesion. The examination of spinal fluid is valuable, as it gives very delicate reactions, although it does not seem to possess as much binding property as does the blood serum. It compensates for this, however, by not containing any complement, nor does it tend to develop anticomplementary actions in any way as extensively as occurs in blood serum. It therefore requires no devitalization, a process which considerably reduces the potency of the substances which produce a positive reaction.

It may well be wondered why any syphilitic infection can remain dormant in a spinal cord or other tissue and only after many years begin to produce its effect. Tubercle, however, may do the same thing, and some modifications in the subject's condition may be responsible for the sudden active development of the infective agent. Syphilis also may produce its effect slowly, and only after extensive damage are the lesions manifested clinically.

Other nervous diseases, such as amyotrophic lateral sclerosis, dementia præcox, disseminated sclerosis, syringomyelia, alcoholic psychosis, cerebral tumors, epilepsy, etc., are not related to syphilis, if one may judge by the negative reactions which they almost invariably present.

In diseases of the cardiovascular system, many questions at issue have been decided by this reaction. Cases of aneurysm, for instance, where the relation to syphilis has long been advocated, give positive reactions in about 70 per cent. of cases. It is also remarkable the frequency with which aortic incompetence is related to syphilis, as 72 per cent. are positive. Aortic incompetence in the majority of cases is syphilitic in origin, and therefore different in its etiology from mitral valve disease, in which the Wassermann reaction is generally negative. All other cardiovalvular lesions excepting aortic incompetence give only 24 per cent. of positive reactions. Even this latter figure undoubtedly shows the high incidence of cardiac disease in syphilis. Mesaortitis, or syphilitic

aortitis, occurs in about 82 per cent. of paretics, but in only 10 per cent of all syphilitics, and this therefore is as truly a parasyphilitic lesion as tabes or paresis. It is the essential lesion which is the precursor of most cases of aortic aneurysm, as only few of such aneurysms result from the ordinary form of arteriosclerosis.

Of all cases of srteriosclerosis only about 12 per cent. give positive reactions, showing that this disease may be produced by many other factors even as common or more commonly than by syphilis; and also that aneurysm in nearly every case has a syphilitic basis.

When we find it reported that in all cases of keratitis, exclusive of suppurative cases, 84 per cent., in iritis 38 per cent., in retinitis and in choroiditis 26 per cent., give positive reactions (Leber), the importance of this test in diseases of the eye is evident, particularly as an indication for therapeutic measures. Similarly it has been shown that ozena is generally, but not always, of syphilitic origin.

Before any application of the serum test for syphilis is made in relation to the diagnosis and treatment of the disease, the general biologic principles involved in the reaction, as well as the method of technique, must be thoroughly appreciated. It is essentially a laboratory method, and is only of value in the hands of trained serologists, as there are innumerable possibilities of faulty technique which may materially modify the result. It is not the comparatively simple process it was originally conceived to be, supposedly depending on the union of a definite syphilitic and antisyphilitic, antigen and antibody, mixture. The first antigens used were derived from syphilitic tissue, yet it has been shown that fatty extracts from normal tissues are capable of giving similar results.

One of the more common factors responsible for the discrepancies in the percentage of positive cases is variation in the quality of the antigen employed, and it is still a debatable point what variety of antigen is the most specific. It is undoubted that the use of a correctly standardized antigen, thoroughly tested for its specific properties, and which in comparatively large amount is neither hemolytic nor anticomplementary, will largely increase the efficiency of the test. In my own experience I have used watery and alcoholic extracts of syphilitic liver, as well as similar extracts of normal tissues; but have found that fatty extracts fractionated by alcohol, ether, and acetone, according to the method advised by Noguchi, gave materially the most reliable results. Such fractionated antigens made from syphilitic liver and normal ox heart seemed of practically equal value in giving specific reactions. Many authorities, however, obtain the best results with extracts of syphilitic tissue. Antigens, as a rule, retain their properties for a considerable time, but after several months tend to deteriorate and become less specific.

The reaction then seems to depend on the development in the

serum of syphilitic cases, of certain antilipoid substances, or, as has been suggested, of substances which have the power of destroying complement. It indicates, so far as can be determined, clinically and experimentally, an expression of the activity of the Spirochæta pallida, and is not therefore a true index of immunity against syphilis. The presence of antispirochete immune bodies can be determined by using an antigen made of spirochetes. The reactions obtained by lipoid and spirochete antigens do not quite correspond, as the latter is much more limited in its range of positive reactions, almost none being obtained in the primary stage, and only rarely in the secondary. Positive reactions obtained with pallida antigens are particularly obtained in latent and tertiary syphilis. They seem to follow more closely the results of the cutaneous reactions produced by luetin, which is an emulsion of dead spirochetes.

Although by no means such a source of variation in the results reported by different workers, as might occur from many other details of the technique of this reaction, the merits of the several hemolytic systems have occasioned considerable dispute. The only systems in common use are the human, sheep, and ox, and each has its adherents. I have used all three, and found no great variation in the results. The most difficult reactions to interpret have been in the use of the human system, and with this indicator there have been more doubtful results than with either of the other systems. Even with careful washing of the corpuscles in preparing the hemolytic amboceptor, a certain amount of precipitation seems to occur with certain serums, which may considerably obscure the result.

With the sheep system a clear cut reaction is usually obtained, yet with this also there are certain difficulties. In my series of reactions over 90 per cent. of human sera contained some natural antisheep hemolytic amboceptor. About 35 per cent. contained between one and two units in 2 c.c. serum, and over 50 per cent. contained more than two units. Most varied between two and four units, yet some contained as many as seven, twelve, or even twenty units. Any marked excess of hemolytic amboceptor will in many cases convert a weak yet truly positive into a negative reaction. It is important therefore to recognize that in nearly half the cases the addition of extra artificial antisheep hemolytic amboceptor is unnecessary, and would tend to increase the number of negative results, as the requisite two units are already contained in the serum. By standardizing this natural antisheep hemolytic amboceptor, contained so frequently in human sera, and where it exceeds two units, if the further addition of amboceptor be omitted about 9 per cent. more positive reactions will be obtained. These extra cases are those in which the specific agent in the serum was comparatively weak, yet they indicate definite evidence of syphilis,

as can be substantiated clinically and by doing a parallel series with an ox system. The delicacy of the sheep system may still further be improved by removing all the natural antisheep amboceptor from the human serum, by saturation with sheep corpuscles until all the hemolysis possible has occurred. By this means the possibility of negative results being produced by sera containing over two units of natural antisheep amboceptor may be avoided.

Perhaps the most reliable indicator is the ox system. This has been used by Browning, Peters, and others, but for some reason or other has never been very extensively adopted. It has, however, many advantages, as only 1 or 2 per cent. or practically no human sera possess any natural anti-ox hemolytic amboceptor. It also gives clear-cut reactions, and judging from its parallel use with the other systems, and the support of clinical evidence, is in my experience at least, the most specific. In the use of this ox system there is one factor which must be recognized, that ox corpuscles require a much longer period for sensitization with their corresponding amboceptor than do the sheep or human corpuscles. Incubation of the amboceptor and corpuscle mixture at 37° C. for half an hour, however, generally insures complete sensitization.

The standardization of the complement, the recognition and the removal of anticomplementary bodies in the human sera, besides numerous other details of technique, make this reaction one of extreme delicacy and reliability. Too often, however, it is conducted without a thorough appreciation of the numerous possibilities of error, and it is probable that variations in the method technique, as well as differences in the class of cases examined, have largely been responsible for the discrepancies reported in the results of the Wassermann reaction.

Although the biologic principles involved are still more or less unknown, yet clinical experience had practically established this reaction as a reliable indication of syphilitic infection. The severity of the systemic infection can also to some extent be gauged by the estimation of the degree of the positive character of the reaction. If efficiently conducted it is almost specific, only very few other diseases being associated with positive reactions, and these irregularly. Cases of leprosy are credited with between 10 and 70 per cent. of positive reactions. Noguchi found it positive in 72.4 per cent. My own experience is limited to three cases, all of which were negative. In scarlet fever, also, reports vary extensively from 1 to 50 per cent., Swift finding 5 per cent. and Fua and Koch 12 per cent. In yaws and trypanosomias the Wassermann reaction is also described as frequently positive, so also in some occasional cases of anemia, tuberculosis, cancer, lymphadenoma, leukemia, etc. Since the discovery of the reaction, improvements in technique have,

however, greatly improved the specificity of the reaction, and considerably fewer positive reactions are now obtained in other diseases than syphilis, so that for all practical purposes the finding of a positive reaction indicates a diagnosis of syphilis.

The value of a negative report, although important, is not quite so definite. A positive reaction may occasionally be delayed until the second week of the secondary stage. The disease may be the result of syphilis, yet exist in a healed condition where there is no spirochete activity. Occasionally also in some acutely syphilitic cases the serum may be negative, as if the spirochetes were not sufficiently active to produce a positive reaction. In such cases the diagnosis of syphilis does not have to stand on the report of the Wassermann reaction alone. A negative reaction may also be the result of recent treatment. Also the binding substances in the serum may be in such small amounts that the preliminary devitalization of the serum reduces them until they are insufficient to produce a positive reaction. Such weak reactions are commonly encountered in the late stages of treatment. Negative reactions may also be readily produced by imperfect technique.

As the greater certainty of the Wassermann reaction in its technique and specific relationship to syphilis has become more thoroughly established, the treatment of syphilis is now largely guided by the results of the serum tests, a positive reaction being held as indicating the presence of active spirochetes in the body. It has provided a method of making a certain diagnosis of syphilis in a much earlier stage than was formerly possible. Efficient treatment can therefore be commenced much sooner, when the disease is more readily influenced, and also with the natural result of lessening the possibility of future development of tertiary syphilitic lesions. Some few cases still seem to resist the most active treatment and develop tertiary lesions. Yet with the methods of treatment at present adopted, tertiary, latent, or late syphilitic manifestations should be eliminated. Certainly the longer the commencement of treatment is delayed the greater difficulty will be experienced in permanently removing a positive reaction from the serum, and until this is done the patient cannot be pronounced cured. It can be shown that even minute traces of mercury bichloride can destroy the binding substance in a syphilitic serum, *in vitro*. It is therefore not to be wondered at that even after short courses of treatment the number of positive reactions is greatly reduced. One negative result is then of little importance, especially if it occurs in course of treatment. If treatment is stopped the activity of the spirochetes recommences and a positive result can again be obtained. Repeated negative results, however, at intervals after the cessation of the treatment, indicate the probability of a final cure. A serum should not be examined for the Wassermann reaction before one month after

the cessation of treatment, as negative results before this are of little importance. A negative result six months after the termination of the course of treatment would seem to indicate a cure. If, however, the reaction has again become positive an entire new course of treatment must be instituted. In latent cases, in which the reaction is recognized as positive some years after syphilis has been acquired, the treatment often has to be very vigorous and prolonged before the serum becomes permanently negative. An interesting finding, and one which is sometimes of use in doubtful cases, is that after an injection of salvarsan in a recently treated syphilitic presenting a negative reaction the serum may again become positive for a short time, as if the drug temporarily stirred up the activity of the spirochetes in the tissues. The time after which treatment causes the reaction in the serum of a syphilitic case to become negative varies with the severity of the case, the stage of the disease, and the extent of treatment. Sometimes two or three doses of mercury cause a temporary disappearance of the binding substance in the serum. In others very extensive treatment has to be pursued before the reaction becomes negative. The result of experimental and clinical experience seems to warrant the assumption that the appearance of a positive reaction in the serum is coincident with a systemic syphilitic infection. It indicates that treatment should be actively pursued, even though the subject is apparently in good health. It has therefore given a method by which a large percentage of the serious after-results of syphilis, such as aneurysm, aortic incompetence, tabes, paresis, keratitis, and the birth of syphilitic children, may be prevented.

Even if any such untoward results have occurred, there is now a considerable amount of evidence that their progressive character may be arrested by antisyphilitic treatment. Such damage to the bloodvessels as occurs in aneurysm or to the nervous system in tabes and paresis is of course permanent, but if the progression of these diseases can be stopped, then a great advance has been marked in their treatment. Also in the case of tabes, the undamaged portions of the cord may assume a considerable proportion of the functions which have been impaired by destruction of certain tracts. Thus reëducation exercises may largely improve the clinical condition of the subjects of this disease after its progressive character has been arrested. That some cases of late syphilis present negative reactions it is also of importance to recognize, as it prevents the indiscriminate administration of antisyphilitic treatment when the disease is already stationary and a healed process, and in which specific treatment would be of no avail.

The study of the Wassermann reaction in the last few years has shown that by the older methods of treating syphilis only in about one case in four was this successful.

Some cases were undoubtedly cured, in others treatment was

unnecessarily prolonged, but in the majority the infection persisted and if the disease was not eventually eradicated by natural means, then late syphilitic manifestations were liable to occur.

The serum diagnosis of syphilis has demonstrated the inefficiency of mercurial treatment by internal administration. It has led to the discovery of the great tolerance which the intestine may acquire to this drug, so that after a time its only effect is to impair the nutrition of the patient. As Fordyce has stated: "Day after day we see patients the victims of paresis, tabes, etc., all giving identical therapeutic history of having had internal mercurial treatment for two or three years. The method stands condemned by its eloquent results."

It has shown the efficiency of treatment by salvarsan and neosalvarsan and also that combined with hypodermic injections of mercury salts; it is better than either alone. Although the hypodermic administration of mercurial preparations is greatly superior to internal treatment and may cause a very rapid disappearance of the external evidences of syphilis, yet only very slowly and often uncertainly, does it effect a cure, as judged by the frequent persistence of positive serum reactions.

With the aid of the Wassermann reaction syphilitic cases can be managed so that there is the least danger of relapses or the development of complications. It has therefore been one of the most important factors in the adoption of the present, earlier commenced, more rapidly effective, more certain, and more scientific methods of treatment.

DIAPHRAGMATIC HERNIA, WITH REPORT OF A CASE.

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Interest in diaphragmatic hernia has been greatly stimulated since the recognition of the condition has been so much facilitated by the development of Röntgen-ray technique. Although the lesion is not a remarkably rare one, until recently the diagnosis had but seldom been made, owing to the difficulty of correctly interpreting its physical signs. Grosser,[1] for example, in 1899, was able to collect records of 433 cases, but Arnsperger[2] makes the statement that up to 1908 the condition had been recognized during life in not more than 10 instances. Now, however, by

[1] Wien. klin. Woch., 1899, No. 24, p. 655.
[2] Deutsch. Arch. f. klin. Med., 1908, xciii, 88.

means of radiography, intrathoracic conditions can be studied much more effectively, and it is possible not only to determine the presence of a diaphragmatic hernia with certainty, but in many instances to ascertain its exact nature. It is probable that the condition is much commoner than the number of published cases would lead one to suppose, for frequently, as in the case of the patient forming the subject of the present report, hernias of even the most extreme type give rise to no subjective symptoms and are revealed only as postmortem surprises should an autopsy be performed for some other reason.

True diaphragmatic hernias, like those involving other portions of the abdominal parietes, consist of protrusions of abdominal viscera through congenital or acquired openings. The definition requires the presence of a sac, composed in this instance of a layer of peritoneum and one of pleura. Such protrusions, through the diaphragm, can take place either when one of the preformed foramina is abnormally wide from birth or gradually becomes so, or when, owing to deficiency or weakness of the muscle bundles, a weak spot exists through which the abdominal viscera can force themselves. This process is, of course, facilitated through the state of latent negative pressure constantly existing in the thorax. Accordingly, such protrusions of peritoneum forming a sac and passing through a hernial ring in an uninjured diaphragm are termed diaphragmatic hernias. It has been customary, however, to speak also of diaphragmatic hernia in those cases in which abdominal organs have entered the thorax through an actual aperture in the diaphragm, either natural or traumatic in nature. Under these conditions no real sac exists and the invading structures are free in the chest cavity, but the clinical manifestations are essentially similar and the term "false hernia" is applied. Diaphragmatic hernias may also be classified as congenital or acquired, and, finally, it is necessary to consider a condition clinically resembling a hernia and known as diaphragmatic eventration. In this, one-half of the diaphragm becomes greatly relaxed, so that the abdominal organs encroach upon the thoracic cavity and a hernia is simulated. The diaphragm remains intact, however, and there is no sac or hernial ring. Before discussing the symptomatology and diagnosis of these various conditions it will be well to go a little more into detail regarding the separate forms.

1. *False Congenital Diaphragmatic Hernia.* This is by far the commonest of all the diaphragmatic hernias, and according to Liepman[3] forms 87 per cent. of the congenital hernias. It results from imperfect development of the diaphragm, so that an opening of greater or less size permitting free communication between the thoracic and abdominal cavities exists from birth. In one case

[3] Arch. f. Geburtshülfe, 1903, lxviii, 780.

reported by Klebs (Eppinger[4]) the diaphragm was totally absent, yet the child lived to the sixth year. Usually, however, the defect is much less extensive, and it is commonly situated on the left side. The opening is most often found in the space between the costal and lumbar portions of the diaphragm. Gössnitz[5] has shown by studies in comparative anatomy that this area is developmentally the last portion of the diaphragm to be closed, and he found that small defects invariably occur in this situation. The larger the opening, the greater is the involvement of the lateral and, finally, of the ventral areas of the costal portion of the diaphragm. In extreme cases almost the entire left half of the diaphragm may be missing, only a vestige of muscle extending from the sternum laterally to the chest wall. The various grades of congenital defect, therefore, may be regarded as different degrees of arrested development. Occasionally, however, defects originating in the sternal portion are seen, and the occurrence of several small sharply circumscribed openings in situations bearing no relation to the development or the anatomical structure of the organ has also been described.

The influences which are operative during intra-uterine life in impeding the normal closure of the diaphragm are not clear, and of the various theories advanced that of Laterjet and Jaricot[6] is perhaps the most plausible. They point out that the portion of the diaphragm that is the last to close is the most poorly vascularized, and that a slight degree of abnormal pressure here would suffice to cause nutritional disturbances leading to an arrest of development. The fact that the right side is almost never involved —Dietlen and Knierim,[7] in 1910, reported the first case of right-sided defect diagnosticated during life—lends color to the belief that the presence of the liver may serve in some sense as a protective agency in preventing disturbances of development.

2. *True Congenital Diaphragmatic Hernia.* This requires that a complete closure of the septum transversum shall have taken place, so that a true hernial sac is formed with a layer of peritoneum on the one side and one of pleura on the other. In other words, a congenital arrest of development occurring at a later period than in the preceding group leads to a thoracic protrusion of the most recently closed and, therefore, weakest portion of the membrane, before there has been a growth of muscle sufficient to resist the pressure. The sac is usually very large, invading a considerable portion of the thoracic cavity, and most often contains stomach and intestine, sometimes even portions of liver and pancreas.

[4] Allgemeine und specielle Pathologie des Zwerchfells. Supplemente zu H. Nothnagel's Specielle Pathologie und Therapie. Wien und Leipzig, 1911. (Contains an elaborate chapter on diaphragmatic hernia and extensive bibliography.)

[5] Inaug. Dissert., Jena, 1903.

[6] Bibliographie anat., 1909, xviii, 22.

[7] Berl. klin. Woch., 1910, No. 25, p. 1174.

3. *True Acquired Diaphragmatic Hernia.* This consists of a protrusion of peritoneum through a hernial ring, which is formed either by the dilatation of one of the natural foramina, or, very rarely, by the giving way of a circumscribed weakened area acquired after birth. Hernias have been observed through Larrey's sternocostal space, through the triangular space described by Bochdalek, bounded by the outer lumbar crus, the adjoining costal portion, and the last rib, through the esophageal foramen, and through the opening for the sympathetic trunk. No hernia has yet been described as occurring through the aortic opening or that for the vena cava.

4. *Acquired Perforations of the Diaphragm* result not in true hernias but in a prolapse of abdominal viscera into the thorax, and so give rise to false traumatic hernias. They may be produced in two ways: either by penetrating stab or gunshot wounds, or by blunt violence causing rupture of the diaphragm. Of these, the former is far commoner; thus Iselin[8] found that of 90 cases 76 were due to stab wounds. The course in such cases is varied: death may follow in consequence of other complications, or closure of the opening through adhesions to neighboring organs may take place. Spontaneous closure of the opening is unlikely and the non-fatal cases usually end in chronic traumatic false hernia. The prognosis of operative closure by suture is good. Rupture of the diaphragm without external wounds may be caused by such injuries as being run over, falls from a height, crushing accidents, railroad buffer accidents, etc. Here again the left side is most affected, the proportion varying according to different authors from 15 to 1 to 4 to 1. Bell[9] has reported a case of long standing in which a nodule of liver with a constricted neck was found projecting through an old rent in the diaphragm apparently not due to an external perforating trauma.

In a third small group of cases rupture has been caused by violent vomiting. An instance of this is described by Daxenberger,[10] in which a man, aged twenty-three years, died sixteen hours after a violent vomiting attack. At the autopsy the stomach was found greatly dilated, owing to an old cicatricial stenosis of the pylorus, and was prolapsed through a fresh rent in the diaphragm. Perforation of the diaphragm due to suppurative processes such as subphrenic abscess, empyema, suppurative pericarditis, etc., seldom leads to hernia owing to the adhesions always present.

5. *True Atypical Traumatic Hernia.* This is a rare type, in which there is a true hernial sac, but the ring is not situated at one of the physiological openings. The protrusion takes place through a weakened spot in the diaphragm, which must still be covered

[8] Deutsch. Zeitschr. f. Chir., 1907, No. 88, p. 150.
[9] Amer. Jour. Med. Sci., 1909, cxxxvii, 581.
[10] Münch. med. Woch., 1906, No. 7, p. 313.

with peritoneum. Schlatter,[11] in 1901, reported a case in which a stab only partly perforated the diaphragm and a hernia followed. Engel, Luksch, and Cruveilhier (Eppinger[12]) have described somewhat similar cases.

6. *Diaphragmatic Eventration, or Diffuse Relaxation of the Diaphragm.* This is not a hernia at all, but the differential diagnosis is often so difficult that the condition must be considered with the hernias. The relaxation of the diaphragm may be so extreme that its dome-shaped summit reaches the level of the second rib. It is practically always left-sided, and in 1910, Dietlen and Knierim[13] said that no instance of right-sided eventration had ever been reported, but Eppinger[14] has since then performed an autopsy on such a case. In consequence of the enormous dilatation the diaphragm naturally loses its muscular quality and becomes converted into a fibrous membrane, with occasional muscle bundles streaking inward from the periphery.

Although Laennec appears to have seen a case of this lesion, and it was Petit who gave it its name early in the last century, only 20 cases have been reported. Its pathogenesis is obscure and most authors assume a congenital predisposition, associated in some cases with degenerative changes in the muscle fibers. The liver seems to act as a protective barrier in preventing the occurrence of the relaxation on the right side. Partial relaxations involving only a portion of the left side of the diaphragm have also been described as diaphragmatic diverticula.

From what has been said it follows that the various lesions described may be classified as follows:

I. True hernias: (*A*) True congenital hernias in which pleura and peritoneum form the sac and only the muscular or tendinous layer of the diaphragm is absent. (*B*) True acquired hernias. (*a*) True typical acquired hernias with the ring originating at one of the natural foramina. (*b*) True atypical acquired hernias with the ring developing in a situation other than at one of the natural foramina.

II. False hernias: (*A*) Congenital false hernia through a congenital defect. (*B*) Acquired false hernia due to traumatic perforation of the diaphragm and either acute or chronic

III. Diaphragmatic eventration due to relaxation of the diaphragm and either involving an entire half of the diaphragm or localized in the form of a diverticulum.

DIAGNOSIS. It is almost inconceivable that extreme dislocation of organs that like the stomach and intestine are undergoing constant alterations in size can exist for years without giving rise to any subjective disturbances, yet such is the case and in many

[11] Münch. med. Woch., 1901, No. 48, p. 34.
[12] Loc. cit.
[13] Loc. cit.
[14] Loc. cit.

of the instances reported the abnormality has been revealed only at the autopsy. This, of course, is true especially of the congenital defects, which frequently give rise to symptoms only late in life, often as the result of apparently negligible inciting causes. Instances have been described in which the previously unsuspected condition was made manifest after dancing, exertion, exposure, or loss of flesh, but on the other hand, some of the patients have never been free from symptoms. Petit's patient, for example, died at the age of forty years after a history of constant attacks of vomiting, dyspnea, and pain, one of which finally ended fatally.

The physical signs in cases in which the hernia is large are usually significant and often conclusive. On the other hand, if the sac is small and centrally placed the diagnosis may be very difficult. The displacement of the heart to the right is very common and should always lead to the suspicion of some form of diaphragmatic hernia if the more usual causes of dextrocardia can be excluded. Since the hernial contents are always largely made up of stomach and intestine tympany can be elicited where normally there should be pulmonary resonance. The area over which it is heard varies at different times, or on changes of position in accordance with the variations in the amount or level of the contained fluid. The breath sounds are absent except at the edges of the area where the lung is in contact with hollow viscera and here there may be a metallic or amphoric quality to the respiratory murmur. Frequently gurgling sounds are present, similar to those heard on auscultating the abdomen. Succussion may be obtained at times, but it is characteristic of this as of other physical signs that it depends on the condition of distention with gas or fluid of the organs at the time of examination. Respiratory changes in the line of pulmonary resonance at the base behind, and Litten's diaphragm phenomenon may or may not be present depending on the mobility of what remains of the diaphragm. The affected side of the thorax is usually larger, the intercostal spaces are filled out, and there may even be respiratory protrusion between the ribs, especially in children. The patients frequently cannot lie on the healthy side because of the resulting cardiac distress, which as well as dyspnea and cyanosis may be brought on by very slight exertion. The abdomen may or may not be retracted, and if the spleen forms part of the protrusion its area of dulness will, of course, be absent. The stomach cannot be located in its usual situation by the customary methods of inflation, etc., and the sharp kinking of the esophagus makes the introduction of the stomach tube difficult or impossible. The same condition gives rise to the so-called dysphagia paradoxa, sometimes present, which consists in the fact that large masses of food are swallowed more readily than small well-chewed mouthfuls which cannot so well be pushed along by the distended esophagus. The dis-

placed stomach usually swings about completely so that its greater curvature is uppermost, but there is great variability in the degree of the subjective gastric disturbance. Frequently a sensation of fulness and oppression in the thorax is complained of after eating.

Hematemesis is a common symptom, and may be due to congestion, incarceration, or ulcer. The thoracic dislocation of the colon may be ascertained by the changes in the physical signs following inflation or the administration of high enemas. Constipation is a common symptom.

Parasternal hernia is the commonest of the true hernias and occurs most often in stout middle-aged persons owing to the invasion of Larrey's space by adipose tissue. A significant sign of the lesion is a gurgling sound heard over the sternum synchronously with the heart beats. There may be a tympanitic quality to the percussion note in the same situation. Paraesophageal hernia is often accompanied by dysphagia, and the introduction of bougies into the stomach may be painful, difficult, or impossible. Eppinger[15] speaks of a ringing musical murmur accompanying the first heart sound as an important sign.

The most important feature in the examination is, of course, the use of the Röntgen ray, but it is necessary to make many examinations, at different times, in different positions, from different angles, and with and without the use of bismuth. Some authors, like Hirsch,[16] have found the pictures obtained after the introduction of a mercury-filled stomach tube especially significant. Giffin[17] emphasizes the obliteration of the distinctly dome-like outline of the normal diaphragm. Eventration and hernia through a large congenital defect, while anatomically totally different conditions, may clinically resemble each other so closely as to make the differential diagnosis extremely difficult or impossible. All the recent writers emphasize the value of radiography in distinguishing between the two. In eventration the shadow of the distended diaphragm is to be seen as a delicate line arching across the summit of the protruded mass of viscera, an appearance that is lacking in cases of hernia. Beltz[18] suggests that in difficult cases it may be possible to make the diaphragm shadow visible separately by slowly filling the stomach with air in different positions. A differential sign to which some authors attach importance is that if there is a defect of large size there is inspiratory elevation of the prolapsed viscera, while in eventration the fluoroscope shows an appearance approaching the normal inspiratory descent of the diaphragm. With the same idea in view, Hess and Jannin[19] suggest observing on the fluoroscope the effect

[15] Loc. cit.
[16] Münch. med. Woch., 1900, No. 29, p. 996.
[17] Annals of Surgery, March, 1912.
[18] Münch. med. Woch., 1910, No. 19, p. 1006.
[19] Deutsch. med. Woch., 1906, No. 49, p. 1990; Verhandl. d. Kongr. f. innere Med., 1906, p. 359.

of electrically stimulating the phrenic nerve, but adhesions between the viscera and diaphragm may make even this test unreliable. Eppinger,[20] indeed, comes to the conclusion that there is no single sign that can be accepted as positive evidence of eventration.

In the differential diagnosis such conditions as pneumothorax, subphrenic abscess, subphrenic pyopneumothorax, and esophageal diverticulum must be thought of and eliminated.

In spite of the usually large size of the ring, incarceration occurs in 15 per cent. of the cases. It is brought on by such conditions as torsion of the viscera, the taking of large quantities of food or fluids, increased intra-abdominal pressure caused by vomiting, straining at stool, or parturition, falls or abdominal contusions, etc. Or adhesions may form about the prolapsed viscera so that peristalsis is interfered with, giving rise to pain or other symptoms, and perhaps eventually to incarceration. Volvulus of the herniated intestine has also been known to occur. The symptoms are those usually seen in cases of incarceration at other hernial openings. If they appear in those previously suspected of having a diaphragmatic hernia, the diagnosis of hernia is confirmed, but when, as is sometimes the case, the incarceration is the first sign of any anomaly it may be a matter of much difficulty to ascertain the site of the lesion. Displacement of the heart to the right may give a clue, and the pain is said to be characteristic in that it extends through the chest with its point of maximum intensity below the hypochondrium, and is increased in inspiration. Girdle pain and dysphagia are sometimes observed. The intestinal obstruction may lead to distention of the abdomen or thorax, the latter, of course, being very significant. Dysphagia and hematemesis are common. Some patients give a history of numerous slight attacks of incarceration; others die of shock in the first attack, or from peritonitis following gangrene of the strangulated viscera.

It is difficult to be definite in speaking of the prognosis other than to say that in general it is that of all hernias, for even in cases in which there are no symptoms the menace of incarceration is always present. On the other hand the discovery at autopsy of a diaphragmatic hernia in an individual who never experienced any discomfort from the abnormality shows that in a certain number of cases the outlook is perfectly favorable. Patients in whom the existence of the condition is ascertained should be told of its nature and be warned of the possibility of incarceration. Eppinger[21] makes the suggestion that some generally understood symbol should be branded on the abdomen of such persons to serve as an indication to the surgeon who might at some future date be confronted with the puzzling picture of incarceration. In eventration the prospects are better, but even here intestinal obstruction may follow. In the traumatic cases the prognosis, of course, depends

[20] Loc. cit. [21] Loc. cit.

on the severity of the associated injuries, but any wound of the diaphragm, even if apparently not attended by immediately serious consequences, must be regarded as a matter of great gravity owing to the danger of subsequent incarceration.

As far as treatment is concerned it may be stated of the traumatic hernias that as soon as the existence of a fresh wound of the diaphragm is ascertained immediate operation is indicated. The very prompt prolapse of the abdominal viscera makes spontaneous closure of the opening almost impossible. Iselin[22] found in 90 cases of operation for traumatic hernia collected from the literature that in 56 cases omentum or an abdominal organ presented in the external wound; and in 6 further cases abdominal contents were found in the thorax on opening the chest. In 64 left-sided cases there was omentum in the external wound 44 times, and 5 times in the pleural cavity, and in 5 instances stomach or intestine presented. In only 10 cases was there no prolapse. Prolapse of the omentum is especially important as it appears to be the first structure to enter the wound and then acts as a guide for the colon and stomach, thus favoring their prolapse. In a recent contribution Magula[23] from a study of 190 cases emphasizes the importance of immediate exploration in all cases of perforating wounds of the lower thorax or upper abdomen in order that a possible opening in the diaphragm may be promptly dealt with.

The prognosis is good when a prompt operation is performed, and according to Iselin the mortality depends only on the degree of injury to the gastro-intestinal tract. In non-operative cases the external wound may close and the patient apparently recover, but it is almost inevitable that sooner or later, often after years of freedom from symptoms, a hernia will develop. In operating most authors prefer the transthoracic route as affording better access to the wound in the diaphragm, but, on the other hand, while suture of the opening is more difficult from the abdomen, Iselin[24] points out that when approached from this side injuries to the stomach or intestine are less likely to be overlooked. In some cases the diaphragm was first sutured by enlarging the thoracic wound, and the abdomen then inspected through a laparotomy. The perils of pneumothorax are not considered grave, and at present can be rendered neglible by resort to one of the recent methods of differential pressure. Eppinger[25] found in 1911 that in 115 cases subjected to operation there were 17 deaths; that is, 14.7 per cent. Suter[26] in 1905, gave the mortality as 13.8 per cent., Iselin in 1907, as 16.6 per cent. Death in most cases was due to injuries to the stomach or intestine. In the sutured cases no subsequent hernia has been observed. In 6 cases of rupture of the

[22] Loc. cit.
[23] Arch. f. klin. Chir., 1910, xciii, 581.
[24] Loc. cit.
[25] Loc. cit.
[26] Bruns' Beiträge, 1905, No. 46, part 2.

diaphragm operated on, only 1 recovery was obtained, the deaths being due to the severity of the trauma or to infection.

In chronic hernias the treatment is entirely directed to the prophylaxis of incarceration by restricting the amounts of food and fluids taken at a time; anything likely to bring on vomiting must be avoided, constipation be guarded against, and pregnancy be prevented. Surgery is indicated only in case incarceration occurs. In cases developing shortly after a trauma the thoracic route is preferable, but in long-standing cases it is better to operate from the abdominal side as it is then easier to separate adhesions about the lower surface of the hernial opening. Carson and Huelsman,[27] however, have recently described a successful operation on a congenital hernia in which the seventh, eighth, and ninth ribs were resected.

The following case is a striking example of an extreme instance of congenital diaphragmatic hernia existing without subjective symptoms, death resulting from an independent lesion. The patient was admitted for a surgical condition in January, 1912, to the service of Dr. Abbe, at St. Luke's Hospital, to whom I am indebted for the opportunity of examining the bedside notes. The patient was a Scotchman, salesman, aged forty-seven years, who came to the hospital suffering from abdominal pain and other symptoms referable to a stenosis of the large intestine, with attending peritonitis, which ended fatally. The history included no symptoms that could be connected with the astonishing dislocation of the abdominal viscera which was revealed at the autopsy.

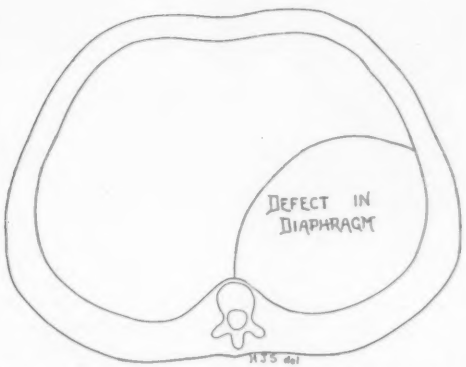

FIG. 1.—Diagram of the diaphragm seen from below, showing position and relative size of the defect.

AUTOPSY. The accompanying illustrations clearly indicate the relations of the displaced organs. On opening the thorax the

[27] Interstate Medical Journal, April, 1912.

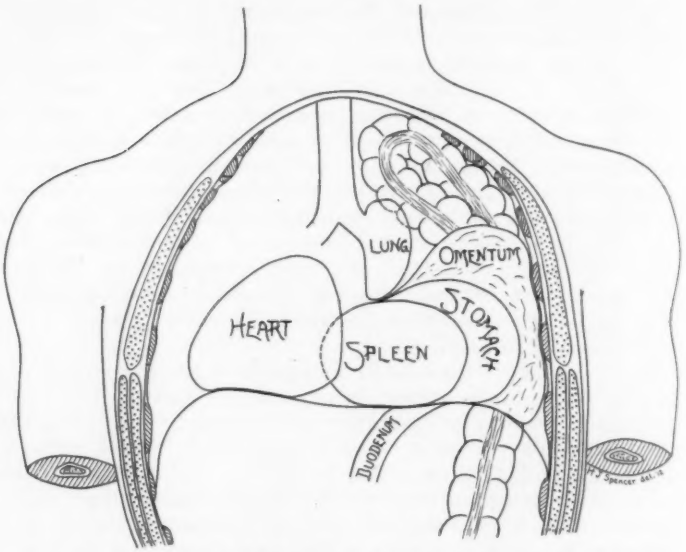

FIG. 2.—Diagram showing relations of the viscera as seen on opening the thorax.

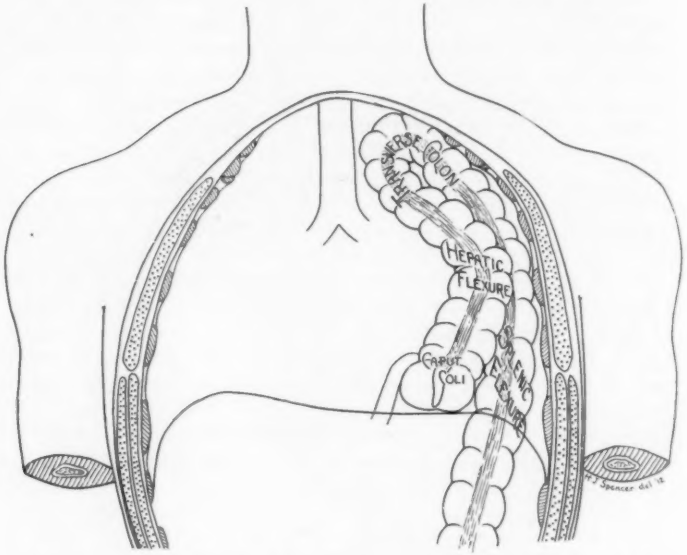

FIG. 3.—Diagram showing the general arrangement of the greatly distended coils of large intestine.

colon was seen occupying the left chest through a left-sided diaphragmatic defect. The spleen weighed 180 grams and was about in the position of the heart. The left lung was collapsed and measured 14 cm. in length, 7 cm. in width, and 2 cm. in thickness. The right lung presented numerous firm adhesions to the chest wall, but was otherwise normal. The left border of the heart was 2.5 cm. to the right of the median line, the right border, 11.5 cm. to the right of the median line, the upper border at the third rib, the apex at the sixth rib, 1.5 cm. inside the mammary line. The left

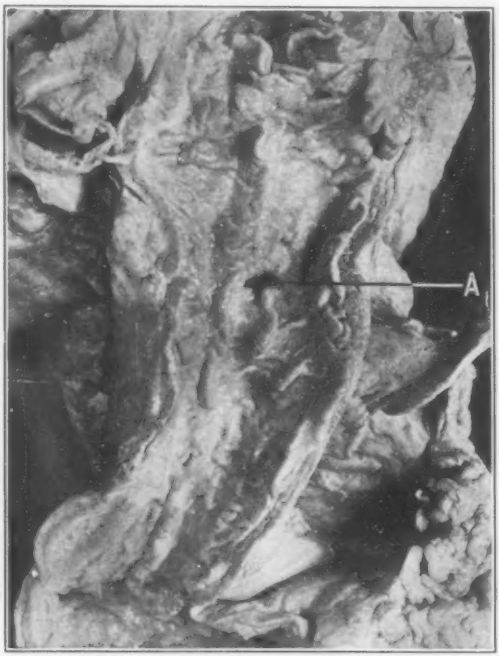

FIG. 4.—Photograph of the portion of the sigmoid stenosed as the result of diverticulitis, with the mouth of the largest pocket shown at *A*.

chest was filled with omentum, caput coli, transverse and descending colon; a few inches of the ileum were lying above the diaphragm. The descending colon was straight and ran directly to the brim of the pelvis. The gut was much distended. The omentum was adherent to the transverse colon, making a sort of bag, but was not in any way adherent to the chest wall. The stomach lay above the diaphragm with the duodenum passing through the opening. The hernia could be easily reduced. The hernial opening occupied the posterior and lateral portions of the diaphragm, was about 15

cm. in diameter, and had rounded and somewhat thickened edges. A loop of small intestine was adherent to the sigmoid at the brim of the pelvis. The sigmoid was constricted for a distance of 5 cm., so that even the little finger would not pass through the obstruction. The muscle was thickened above the constriction. The mucosa was practically normal except for four

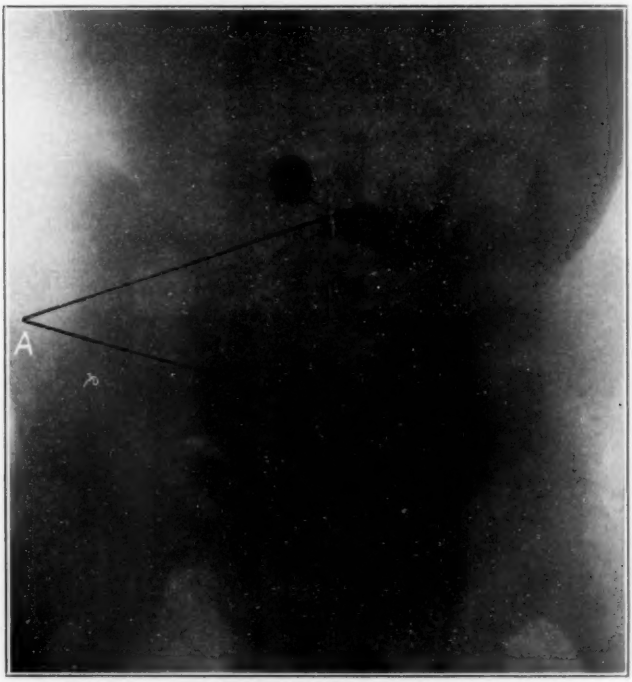

FIG. 5.—Bismuth radiograph showing at *A* the portion of the sigmoid stenosed as the result of diverticulitis.

pockets with mouths 0.5 cm. in diameter. These pockets varied in depth from a few millimeters to several centimeters. There was a thick collar of firm inflammatory tissue some 12 cm. long about the sigmoid just above the pelvic brim, binding the gut down to the posterior abdominal wall. There was a band of fat and inflammatory tissue over the surface of the sigmoid, aiding in the constriction. The other organs presented no abnormalities.

DIAGNOSIS: Perisigmoid inflammation (diverticulitis) with obstruction and beginning peritonitis. False congenital diaphragmatic hernia.

CONCLUSIONS. Diaphragmatic hernia is much commoner than generally supposed, and may exist indefinitely without giving rise to symptoms. Dextrocardia and physical signs suggesting those of pneumothorax should always cause the possibility of this condition to be thought of and lead to careful radiographic study of the thorax.

SOME CONSIDERATIONS REGARDING THE FACTOR OF FATIGUE, WITH REFERENCE TO INDUSTRIAL CONDITIONS.[1]

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WITHIN the past few years considerable literature has grown up with reference to the general subject of fatigue, and more recently it has been sought to utilize the results from the investigation of fatigue in helping to solve some of the industrial and occupational problems. While the mass of literature about these subjects is so large as to make any effort toward reviewing it at this time a practical impossibility, yet from it all there stand out certain general principles to which it is well worth while to call attention. There are certain other fairly well-accepted facts which belong within this same sphere, but which as yet have not received the recognition which is their due, to which attention also may be invited.

In the first place the problem of fatigue has been most thoroughly worked over with reference to the subject of muscular fatigue and with the use of the nerve-muscle apparatus. Here the problem has been a relatively simple one, and yet even with all its simplicity there remains a variety of questions to be answered, and the undisputed conclusions are few. It is generally admitted, as a result of this kind of work, that fatigue has two factors, a negative and a positive: the former the result of an actual wearing out of the used substance, in this case muscle, and the second the result of the formation of certain poisonous substances such as carbon dioxide, paralactic acid, and monopotassium phosphate. The term exhaustion has been proposed for this negative side of fatigue, while the word fatigue itself is used solely by some authors to indicate the positive side.

These results are results of the fatigue of muscle. The question of the fatigue of the nervous system is an entirely different one. As soon as an effort was made to define the actual place where

[1] Read at the International Congress of Hygiene and Demography, Washington, D. C., September 23, 1912.

fatigue occurred in the living animal or the nerve muscle apparatus it was found to be no easy matter. In general, however, it may be said that the nerves themselves do not fatigue, and that the conception of the central nervous organs themselves showing fatigue, as is more particularly set forth by the experiments of Hodge, has changed materially of late years until it is now believed that the central nervous organs, like the nerves themselves, are little susceptible to fatigue. In the case of the nerve-muscle apparatus it would seem as if the nervous tissues were saved from fatigue by the fatigue of the muscle, or that both muscle and central nerve organs are saved from fatigue by fatigue of the motor end plates in the same way that a dynamo may be saved from damage by the melting of a fuse. The classical experiment of Sherrington, which was to the effect that a muscle which is connected with a spinal cord centre, which centre may be reached by several afferent tracts, responds as quickly to stimulation through one of these afferent tracts after one of the others has been so exhausted that no results follow its stimulation, indicates that the locale of the exhaustion is at the synapse between the afferent and efferent neuron, and that, again, the central nervous organs are protected from exhaustion by this synaptic exhaustion just as in the former case they were protected by motor end-plate exhaustion. If these are the mechanisms, then it is readily seen that neither the nerves nor the central nervous system itself can ever be seriously exhausted, that the synaptic junctions and the motor end plates interpose obstacles to the occurrence of any serious disintegrating processes, and therefore are protective devices for conserving the organism.

At this point one cannot resist drawing certain analogies. We have seen that it is fairly well conceded that the motor end plates and the synaptic junctions, by becoming impervious, prevent exhaustion of the central nervous system; so it is commonly accepted that in the mental sphere disorder of attention has the same conservative function. The person who can no longer pay attention is saved from the possibilities of serious exhaustion, and this conclusion is in harmony with the more recent belief, *contra* the original opinions following the experiments of Hodge, that the central nervous organs really do not suffer from exhaustion.

Again, mental fatigue is still more complex. We have no knowledge at all for correlating the symptoms of mental fatigue with any definite changes in the nervous system, and our means of measuring mental fatigue are most of them so complex when one comes to investigate them, and so contaminated by other than mental factors, that it is extremely difficult, in fact almost impossible, to evaluate the results. It is obvious, for example, that such instruments as the ergograph or the dynamometer, the esthesiometer, and the algesiometer all involve both mental and

physical factors, while when we come to take up the question of the symptoms of mental fatigue, we realize that defect of attention is one of them. Then when we realize that the whole attitude of psychology toward attention has been materially changing of recent years, and that attention is being more and more considered as an affective state, as an affective orientation of the individual as a whole toward a stimulus in the environment, the muscles naturally playing a large part, it becomes evident that the difficulties are certainly very great. In the face of these difficulties it would seem that we had better stick to fundamental principles and not mix our categories and so not endeavor to speak of fatigue in one category in terms of fatigue in another. Let the mental and the physical, or as symptoms, called the psychic and the physiologic, remain apart, and endeavor to determine questions of fatigue in the mental sphere purely in mental terms. For this purpose probably the best method is Kraepelin's method of continuous additions.

This much I have said preliminarily because questions of fatigue which arise in the consideration of industrial and occupational problems almost invariably imply fatigue both of mind and of body. It will be seen, thus, that in speaking of fatigue we are using a term of vague connotations, and dealing with a condition that admits of measurement only with the greatest of difficulty. Not only this, but in the present state of our knowledge it is practically impossible to state wherein the fatigue is resident, what part of the individual really is fatigued, and what are the mechanisms both chemical and physical of that fatigue. The general gross fact which seems to issue from this complex situation is that human beings, worked under given conditions, tend to show a gradual falling off in the efficiency of their work, and that this falling off in efficiency can be prevented by changing the conditions, more particularly by increasing the opportunities for rest; and that, further, when human beings continue to work under conditions which show a gradual falling off in efficiency, other manifestations tend to come into evidence—namely, various kinds and descriptions of disturbances of health. So that with our present knowledge it would seem more accurate, and perhaps wiser, to deal with the human being as if he were a machine and with his efficiency as measured by his output and endeavor to find what the conditions are which lower his efficiency, either impairing it temporarily or tending to impair it permanently, and then endeavoring to discover what the conditions are which will prevent this temporary or permanent impairment, and so increase the efficiency.

I have been tempted to say what I have said, which is more especially a plea for greater definiteness in the use of terms, by looking through the literature of fatigue, particularly in connection with various occupations, and noticing with what little regard

for accuracy the term fatigue and certain other terms are used. I refer more particularly to the conditions which are presumed to be the results of mental fatigue. I find numerous papers, some of them by talented writers, showing the prevalence and the increase of neurasthenia and hysteria in certain occupations; and I note the statistics, especially those of foreign sanatoria for the working classes, showing the immense increase in cases of nervous diseases that were admitted to these sanatoria during recent years. There appears to be little in any of this literature that at all adequately accounts for these conditions.

In the realm of the neuroses and the psychoneuroses, such particularly as neurasthenia and hysteria, to which I have called attention, the particular character of the work or its severity could by no possibility operate as adequate causes if our present ideas of these conditions are correct. Hysteria, for example, is a mental disease, dependent upon purely mental causes, in other words, psychogenic in origin. Work of any character, description, or degree of severity could not be conceived to be a cause in any true sense. It is well known that if we have some weak point in our bodies it bothers us more when we are not in good condition, and we are able to adjust ourselves to it better when we are in good health. The muscles of accommodation, for example, partake of the tone of the general musculature, and when health is good they may give little trouble, but when health is poor, they may cause difficulty. In the same way, and only in that way, can occupation or fatigue of any kind be said to be a causative factor of hysteria. It can only be an adjuvant cause at best, and at that, you will see, an unimportant one. With neurasthenia we are dealing with a condition which is not so prominently mental. In fact, neurasthenia, as we understand it today, is not a mental disorder at all, but a physical disorder. However, the term neurasthenia is perhaps one of the most loosely used terms in medicine, and as I see it through the literature that I have spoken of before, there appears to be no definiteness about its use. It is applied to all sorts and conditions of things, including the whole realm of the neuroses and the psychoneuroses, and probably some of the actual insanities. We have a fairly well-defined syndrome to which the term neurasthenia is applicable, the symptoms of which are, in the main, a feeling of pressure on the top of the head, more or less insomnia, spinal irritation with perhaps pain in the back, certain paresthesias, easy fatiguability, and emotional irritability. This may be a primary neurosis or it may be a secondary one following upon other illnesses, such as prolonged sickness of some kind, or succeeding an acute illness, such as typhoid fever. As a primary neurosis it may be described as a primary fatigue neurosis, although it must be realized that the assumption that it is due to fatigue and that the symptoms

are dependent upon the elaboration of toxic fatigue substances is purely hypothetical. Even admitting the truth of all these things, however, there is absolutely no warrant, if our present concepts of this condition are correct, and they are being verified every day, for believing that occupation of any kind or of any degree of severity can be other than a purely adjuvant and unimportant cause of this condition, as is the case in hysteria.

The limits of this paper prevent any extensive illustration of the opinions that I have just brought out with reference to hysteria and neurasthenia. It will be recognized that I have in mind the more recent hypotheses of Prof. Freud, who would place both of these diseases, and a number of others, in the same category—namely, he would ascribe as the necessary etiological factor in both cases some sort of disturbance in the sex life of the individual, so that these diseases become of great importance, not only because they are, as I would call them, social diseases, but because their problems are essentially broader than the individual—they are biological problems. A single illustration will give an idea of how I regard the situation.

It will be seen in the literature, for example, that many of the telephone girls are becoming neurasthenic, and the cause is attributed to long hours of work, the extreme effort of attention that is necessary because of the character of the work, and its constant annoyance and irritating character. All these things are true, but if the modern hypothesis of neurasthenia, to which I have referred, is correct, they cannot be the fundamental causes. To speak broadly we can only understand the neurasthenia in such cases by thinking of these girls as individuals who have been prepared by nature, up to a certain point, to fulfil a certain function; and then because of the exigencies of life, all the energies which have been developed in that direction are, so to speak, side-tracked, and at about the period of puberty, when nature might expect physiological fulfilment, the individual is called upon to make a complete readjustment, to find entirely new avenues of outlet for nervous energy, to concentrate upon entirely alien interests. Some people are so constituted that they can do this thing; as a result they succeed. Others are so constituted that they cannot. They become neurasthenic or develop other neuroses, while certain others, and they are perhaps the most frequent, occupy a borderland position. These girls under favorable conditions of employment, with plenty of opportunity for rest, good food, good housing, etc., manage to get along. With prolonged hours of work and irritating conditions, perhaps coupled with unhygienic and unsanitary living, they break down. So it will be seen what is meant by fundamental causes, and how we regard the usually attributed causes as only adjuvant. It will be seen also why we believe the problem is deeper than the individual, and strikes at once at the

social conditions brought about by the various industries and occupations.

We might speak of other conditions, but these two are sufficiently illustrative. Hysteria surely and in all probability neurasthenia belong to the diseases which are not dependent upon the introduction into or the action on the body of some specific morbific agent. They are essentially social diseases which depend for their existence upon the maladjustment of individuals to their social surroundings, their inability to meet the demands that are made upon them because of their relations to other people, actually or prospectively, and as such these diseases cannot be dependent for their existence upon long hours of work or upon the character of that work. These considerations, however, do not make it any the less important that these conditions be considered in connection with the various industries, nor do they make it obvious why there has been such an increase in the number of these diseases. A moment's reflection will convince anyone that their importance lies not in the fact of their association with any particular kind or character of work so far as the fatiguing qualities of that work may be concerned, but in the fact that they are expressions of causes that are more widely operative, social causes which have invaded and changed the social conditions under which people live, and evidently changed these conditions disadvantageously, so as to make possible the outcropping of these diseases, and investigation of industrial conditions should realize this factor in the situation as exemplified by the presence of this class of diseases.

My plea, then, in this paper is for the recognition of what we have termed social diseases, for a realization that the problem of the various industries, as that problem deals with the question of the health of the workers, is a broader problem than the problem of ordinary physical disease. It is a problem which touches the whole question of society, and which presents for consideration the neuroses and the psychoneuroses as indications of a disease which is not individual, but social. Here we have in this class of diseases a point of attack upon abnormal social conditions, and by their study some kind of idea may be had as to the best means of approaching the faulty social conditions of which they are the expression, and which may be incident to the industrial conditions under consideration.

The necessary restrictions of such a paper as this make it impossible for me to illustrate what I mean except briefly. It has been shown by careful analysis of certain cases of these psychoneuroses that the disorder was dependent upon experiences in the early years of childhood—types of experiences which, in many instances, were dependent upon the general crowded condition in which the families were forced to live. It will be seen, therefore, in such cases that the disorder from which the patient suffers

leads directly back to social conditions, which social conditions may or may not be dependent upon industrial conditions. The psychoneuroses, therefore, may become a good barometer of certain social states dependent upon industrial conditions, and while it is known that the social state of the worker has been investigated fully, still we do not think that it has been appreciated that many of the specific manifestations of illness are outward indications of certain types of social conditions that are undesirable. It will be seen then that a correlation between the work of the psychiatrist and neurologist and the social worker is possible along these lines. This paper merely bespeaks a recognition of the advantage of this correlation, which if pursued would be seen to offer many possibilities for work.

THE TOPOGRAPHY OF THE CARDIAC VALVES AS REVEALED BY THE X-RAYS.[1]

By George William Norris, A.B., M.D.,

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(From the Laboratory of Anatomy of the University of Pennsylvania.)

For many years attempts have been made to determine definitely the exact spots on the anterior chest wall under which lie the valves of the heart. The method by which studies in this direction have been made has consisted of the thrusting of long pins into the thorax and then opening the latter and noting the points at which the pins pierced the heart. From data thus obtained diagrams were constructed which were supposed to depict the valves in their relation to the anterior chest wall. That this method is inaccurate is demonstrated rather forcibly by the lack of unanimity in the descriptions given by various authors. In the following excerpts we present the opinions of a number of authorities, and it is interesting to note that the more superficially located is the valve the more nearly do the different authors agree, while the deeper lies the valve the more widely do the writers disagree.

[1] Read before the College of Physicians of Philadelphia, October 2, 1912.

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[1] Read before the College of Physicians of Philadelphia, October 2, 1912.

Aortic: Behind the junction of the third left costal cartilage with the sternum, one-fourth covered by pulmonary valves. *Pulmonary:* Behind the upper border of the third left costal cartilage and the adjacent part of the second left intercostal space. *Tricuspid:* Behind the left half of the sternum at the fifth costal cartilage and the fourth intercostal space. *Mitral:* Behind the left half of the sternum at the third intercostal space and at the fourth intercostal space.[2]

FIG. 1.—In this *x*-ray photograph every valve is shown with great clearness. On account of cardiac hypertrophy and sinistro-displacement, all the valves lie well to the left of the sternum. *P*, pulmonary valve; *A*, aortic valve; *M*, mitral valve; *T*, tricuspid valve.

Aortic: Behind the sternal end of the third left intercostal space. *Pulmonary:* A little above and behind the third left chondrosternal junction. *Tricuspid:* Behind the middle of the sternum at the fourth intercostal space. *Mitral:* Behind the fourth costal cartilage at the left border of the sternum.[3]

[2] G. A. Gibson, Diseases of the Heart and Aorta, 1898, p. 38.
[3] John B. Deaver, Surgical Anatomy, 1903, p. 409.

Aortic: Slightly below and internal to the pulmonary on the level with the third space between the midsternal and the left sternal line. *Pulmonary:* Behind the sternal end of the third left costal cartilage. *Tricuspid:* On the horizontal line between the two sternal ends of the fifth cartilage at the point intersected by a line drawn from the sternal end of the third left cartilage to the upper border of the sternal end of the seventh on the right. *Mitral:* Behind the sternal end of the third left space.[4]

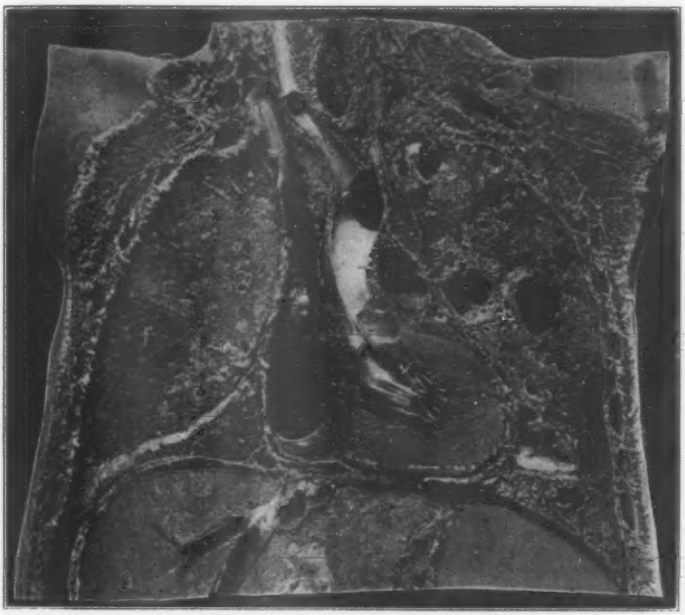

FIG. 2.—Frontal section of the thorax, the *x*-ray picture of which is shown in Fig. 3. The tuberculous cavities of the left lung are well shown in the *x*-ray plate.

Aortic: Lower border of the third left costosternal junction. *Pulmonary:* Upper border of the third left costosternal junction. *Tricuspid:* Just to the left of the midsternal line level with the fourth space. *Mitral:* Fourth left costosternal junction.[5]

Aortic: The third left intercostal space. *Pulmonary:* Third left costosternal junction. *Tricuspid:* Midsternum at the level of the fifth costosternal junction. *Mitral:* Fourth left costosternal junction.[6]

[4] de Nancrède, Essentials of Anatomy, 1911, p. 183.
[5] Henry Gray, Anatomy, Philadelphia, 1908, p. 559.
[6] C. Toldt, Atlas of Human Anatomy, New York, 1904, Part 5, p. 586.

Aortic: Lower border of the third left costosternal junction. *Pulmonary:* Upper border of the third left costal cartilage close to the sternum. *Tricuspid:* Behind the sternum at the level of the fourth interspace and anterior extremity of the fifth costal cartilage extending down to the right almost as far as the sixth chondrosternal junction. *Mitral:* Behind the left half sternum at the level of the fourth chondrosternal junction.[7]

FIG. 3.—*X*-ray photograph of thorax, a frontal section of which is shown in Fig. 2. Of the cardiac valves only the semilunars show with clearness. The tuberculous cavities of the left lung and the internal mammary vessels are well demonstrated. *P*, pulmonary valve; *A*, aortic valve.

Aortic: Opposite the inner lower border of the third left costal cartilage. *Pulmonary:* Upper border of the third left costal cartilage at its sternal junction. *Tricuspid:* Behind the sternum from the opposite fourth left interspace to the fifth right interspace. *Mitral:* Left edge of the sternum at the level of the fourth left costal cartilage.[8]

Aortic: Behind the third intercostal space, close to the left side of the sternum. *Pulmonary:* In front of the aortic valve,

[7] L. B. Rawlings, Landmarks and Surface Markings of the Human Body, London, 1908, p. 37.
[8] C. R. Whittaker, Essentials of Surface Anatomy, London, 1912, p. 29.

behind the third left chondrosternal junction. *Tricuspid:* Behind the middle of the sternum, about the level of the fourth costal cartilage. *Mitral:* Behind the third intercostal space, about one inch to the left of the sternum.[9]

Aortic: Middle of the sternum, at the level of the third costal cartilage. *Pulmonary:* Second intercostal space, somewhat to the left of the edge of the sternum. *Tricuspid:* Midway between

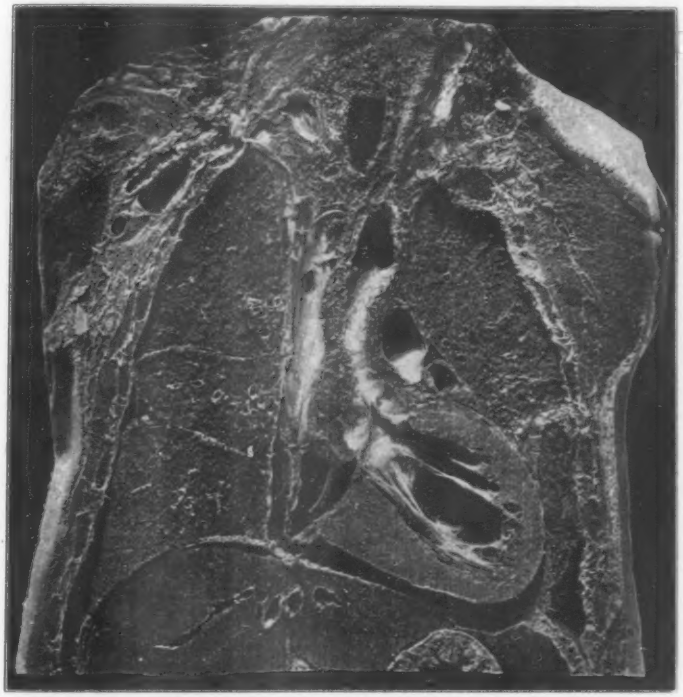

FIG. 4.—Frontal section of the thorax, the *x*-ray picture of which is shown in Fig. 5. There should be noted the cut surfaces of the aorta, the pulmonary artery, and the left auricular appendix, all of which appear clearly in Fig. 5.

the third left and the fifth right chondrosternal articulation. *Mitral:* Beneath the third left chondrosternal articulation.[10]

Aortic: Behind the left half of the sternum at the lower border of the third costal cartilage. *Pulmonary:* At the upper border of the third left chondrosternal articulation. *Tricuspid:* From the midsternum at the level of the fourth costal cartilage to the

[9] John H. Musser, Medical Diagnosis, 1900, p. 595.
[10] Herman Sahli, Diagnostic Methods, 1905 (quotes Luschka), p. 247.

fifth chondrosternal junction. *Mitral:* Behind the left half of the sternum at the level of the fourth costal cartilage.[11]

Aortic: Behind the midsternum at the level of the third intercostal space. *Pulmonary:* Behind the third left chondrosternal articulation. *Tricuspid:* Behind the lower portion of the sternum at the level of the fourth intercostal space. *Mitral:* Behind the fourth chondrosternal articulation.[12]

FIG. 5.—*X*-ray picture of the thorax, a frontal section of which is shown in Fig. 4. The valves in this plate are photographed rather faintly. They are more widely separated than is usually found, the condition being probably due to cardiac dilatation. The aorta, the pulmonary artery, the left auricular appendix (see Fig. 4), the pulmonary veins and the internal mammary and coronary arteries are shown with great clearness. *P*, pulmonary valve; *A*, aortic valve; *M*, mitral valve; *T*, tricuspid valve.

Aortic: Behind the left half of the sternum, opposite the lower part of the third chondrosternal articulation. *Pulmonary:* Behind the third left chondrosternal articulation. *Tricuspid:* Behind the midsternum, opposite the fourth chondrosternal articulation and

[11] J. C. Da Costa, Jr., 1911, p. 298.

[12] Joh. Sobotta, Atlas and Text-book of the Human Anatomy, American Translation, 1906, ii, 172.

the fourth intercostal space. *Mitral:* Behind the left half of the sternum opposite the third interspace and the fourth chondrosternal articulation.[13]

Aortic: Behind the left half of the sternum a little below and to the right of the pulmonary. *Pulmonary:* Behind the sternal end of the third left costal cartilage. *Tricuspid:* Almost behind

FIG. 6.—Frontal section of the thorax, the *x*-ray picture of which is shown in Fig. 7.

the midsternum, opposite the fourth interspace and the fifth chondrosternal articulation. *Mitral:* Opposite the sternal end of the third left interspace.[14]

Aortic: The third interspace close to the sternum. *Pulmonary:* At the unction of the third rib with the left side of the sternum. *Tricuspid:* Behind the sternum, near the middle line about the

[13] D. J. Cunningham, Text-book of Anatomy, 1906, p. 789.
[14] G. A. Piersol, Human Anatomy, 1907, p. 692.

level of the fourth costal cartilage. *Mitral:* Behind the third intercostal space about one inch to the left of the sternum.[15]

Aortic: Behind the inner edge of the third costal cartilage, intercostal space, and contiguous portion of the sternum on the left side. *Pulmonary:* A little higher and more to the left. *Tricuspid:* Below and a little to the left, a line drawn from the inner

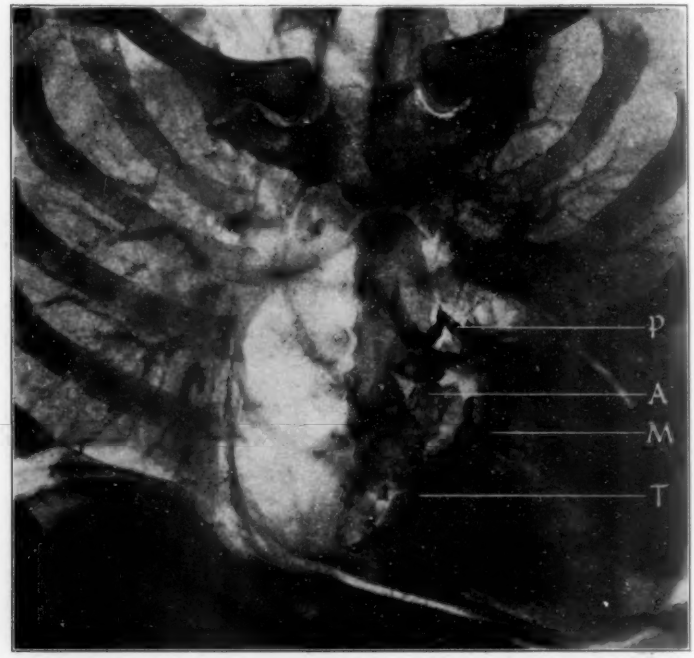

FIG. 7.—*X*-ray picture of the thorax, a frontal section of which is shown in Fig. 6. The individual leaflets of the pulmonary and aortic valves are shown with unusual distinctness. All the valves lie approximately one rib below what is described as their normal position. *P*, pulmonary valve; *A*, aortic valve; *M*, mitral valve; *T*, tricuspid valve.

end of the third costal cartilage on the left to the inner end of the sixth right costal cartilage. *Mitral:* Behind the third intercostal space about one inch to the left of the sternum.[16]

With the view of settling definitely these moot points the present study was undertaken. In the planning of our investigations the problem naturally divided itself into two parts, (1) the preparation of the material so that conditions existing during life would be present for postmortem study, and (2) the depiction of such con-

[15] H. Morris, Human Anatomy, Philadelphia, 1895, p. 972.
[16] J. Leidy.

ditions with all possible sources of error eliminated. In order to secure these desiderata the following plan was evolved: Each cadaver on being delivered at the University of Pennsylvania was injected with 10 per cent. formaldehyde solution and then put into cold storage. When thorough freezing had been secured the head and neck, the upper extremities, and the lower part of the trunk were cut off. The thorax was then cut into frontal sections about one inch thick, the cuts being made parallel with the anterior surface of the chest. Each section was then cleaned up by removing all blood clots and saw detritus from the heart cavities and large bloodvessels. In this manner we avoided distortion, since all parts were hardened in the position which they occupied at death.

To depict the conditions present we adopted the following procedure: Each valve leaflet was carefully dried and then painted with the thickest possible lead paint. This was readily done, for the sections were so thin that all the valves were accessible, and in most instances it was possible to paint both surfaces of the entire eleven leaflets.

Finally, after the valves were painted, the sections were superimposed, with the anterior one below, and an *x*-ray photograph taken. In order to show with greater clearness the relations of the valves to the sternum and ribs, that section of the thorax which comprised the posterior portion and included the vertebral column, the posterior section of the ribs and the thick spinal muscles, was not used. By discarding this portion nothing was lost and much was gained in clarity, since the vertebræ and the posterior part of the ribs were eliminated from the pictures.

In the course of our investigations fifteen bodies were sectioned. It was soon evident, however, that a much larger number would have to be studied before any definite conclusions regarding normal relations could be reached, since many of the cadavers represented pathological alterations in the topography of the thoracic viscera. Often the heart was displaced as the result of extensive pulmonary tuberculosis, or of hypertrophy of the heart. Other lesions, such as pericardial effusions, atalectatic lungs, etc., furnished additional sources of error.

We therefore offer this communication in the nature of a preliminary report, and in demonstration of an entirely feasible and hitherto unemployed method of studying post mortem the topography of the heart valves in health and disease.

In conclusion, we wish to express our indebtedness to Dr. Henry K. Pancoast for his kindness in furnishing us with the *x*-ray photographs.

THE ROLE OF THE STETHOSCOPE IN PHYSICAL DIAGNOSIS.

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The object of auscultation is threefold: (1) It should bring to the ear intracorporeal sonorous vibrations; (2) from the nature of the sound we deduce the physical conditions producing it, and (3) finally we attempt to judge the significance of these conditions to the vital economy of the patient.

Mediate auscultation through the stethoscope is so well established that immediate auscultation by direct application of the ear to the body may well-nigh be numbered among the lost arts. Nevertheless, Conner[1] has called attention to the surprising fact that certain pathological sounds, as the diastolic murmur of aortic insufficiency and the amphoric note from the bronchi, may be missed through the stethoscope while plainly audible with the unaided ear. It is well to have such possibilities in mind when the constant refinement in instrumentation, particularly as manifested in the German clinic, is, as it were, making the methods of physical diagnosis more and more artificial. The designer of a stethoscope is happy to make the sounds which it transmits as loud as possible, yet he may be sure that this loudness is but the result of sympathetic vibration of the instrument itself, and it is hardly possible to construct an apparatus which will at once magnify in equal ratio all the tones that come to it. F. von Müller[2] has recently demonstrated that the normal inspiratory murmur is much lower in pitch than the note obtained from the trachea or bronchi. He used as a stethoscope-resonator a rubber tube whose length could be varied at will. It required a much longer tube to "speak" in response to the murmur of inspiration than to the note from the trachea. It is always to be suspected that any extraordinary intensity of auscultated sound is due to selective resonance on the part of the instrument used. The roar from a bullfrog's pouching chops probably represents inadequately the range of partial tones emitted from his larynx.

It may be admitted, as a general fact, that there is no such thing as a sonorous vibration within the chest, but it comes to the ear modified by the sympathetic resonance and conductive properties of the tissues of the thorax; judgments founded on auscultatory findings represent only the more or less conscious appre-

[1] Certain Limitations of the Stethoscope (Binaural) and Their Clinical Importance, New York Med. Jour., 1907, lxxxvi, 56.

[2] Zur physikalischen Diagnostik, 1911, xxviii, Kong. f. innere Med., 181.

ciation of the way in which sonorous vibrations are modified by definite physical changes in the tissues.

The simple fact of tactile fremitus is a demonstration of the power with which the wall of the chest may reproduce vibrations originating in the larynx. It has been pointed out by Coplin,[3] by the writer,[4] and by others, that certain pathological sounds have their origin in the chest wall itself, though they imitate the sonorous effects of underlying disturbances. The importance of the chest wall as a resonator for visceral vibrations has appealed to me for many years, and the belief has gradually developed that the experimental modification of mural vibrations during physical examination gives unwonted clarity to the perception of the conditions within the thorax. The procedures applicable to the examination of the heart were published in 1897,[5] while a consideration of them in the study of the lungs has recently been detailed.[6]

In brief the method purports to enable the examiner to apprehend at will the sonorous vibrations intrinsic to the thoracic viscera unconfused with those proper to the chest wall itself. This result is accomplished by damping the mural vibrations by pressure applied to the chest piece of the stethoscope. The astounding predominance of the mural component of the sounds to which we are accustomed to listen in the chest becomes especially obvious through the auscultation of those normal lungs in which vocalization is accompanied by considerable tactile fremitus—as in vigorous young men.

The powerful, resonant voicing heard through the stethoscope when applied lightly to the chest is usually turned into a flat, feeble, and distant sound when the bell of the instrument is pressed firmly upon the skin. This effect of stethoscopic pressure is much more marked below the level of a plane transecting the body at about the level of the fourth rib in front. As was pointed out in a previous paper,[7] the vibrations of the air in the trachea and large bronchi penetrate more or less freely directly to the parietes of the upper part of the thorax and are there not annulled by stethoscopic pressure. The sounds heard in the lower parts of the chest are to a much larger proportion made up of sympathetic vibrations of the parietes. This is well demonstrated in the auscultation of the normal inspiratory murmur when it is strongly diffused; pressure usually annuls the murmur over the lower areas, but not above. The normal, breezy inspiratory murmur when not annulled is

[3] Amer. Jour. Med. Sci., 1904, cxxvii, 754.

[4] Sewall, The Origin of the "New-leather" and "Dry-friction" Sounds Heard on Auscultation, Amer. Jour. Med. Sci., 1909, cxxxvii, 364.

[5] Sewall, The Use of Stethoscopic Pressure in Physical Examination of the Heart, New York Med. Jour., 1897, vol. lxvi.

[6] Sewall and Childs, A Comparison of Physical Signs and X-ray Pictures of the Chest in Early Stages of Tuberculosis, Arch. of Int. Med., 1912, x, 45.

[7] Sewall and Childs, loc. cit.

usually greatly diminished by stethoscopic pressure, and is rendered sharper, more bronchial, and higher in pitch. These facts have led me to the revolutionary opinion that the normal inspiratory murmur owes its pitch, volume, and quality chiefly to sympathetic vibration of the chest wall.

The influence of the main bronchi on the transmission of sound was recently illustrated in the case of a right-sided serous effusion which reached to about the level of the middle of the scapula. Whispered sounds were plainly transmitted throughout the area of dulness, but failed just above it. When the fluid was aspirated so that its level fell to about the angle of the scapula the whispered sounds could no longer be heard over the remaining effusion. In the first case probably vibrations were taken up by the fluid directly from the right bronchus and its main descending branches, while in the second case the fluid had fallen below the great air vessels and therefore failed to pick up their vibrations.

When the voice is auscultated over a serous effusion in the ordinary way it may show no specific change in character, but on applying pressure the pitch is raised and the quality and duration of the sound are altered in a characteristic manner.

Now if we may assume that the fundamental tone of the chest wall remains practically unchanged while extensive pathological disorders develop in the viscera, it follows that any modification of auscultated sounds due to alteration of conductivity or resonance in the viscera must be relatively exaggerated by any procedure which annuls the mural vibrations. Stethoscopic pressure dampens the mural vibrations and presents to the ear the real acoustic changes in the viscera. The student will observe that the invariable effect of pressure applied to the stethoscope is to raise the pitch of the auscultated note, apparently by cutting off its fundamental and lower partial tones. It has been pointed out by von Müller[8] that the "chest tones" of the voice, which especially invoke the resonance of the thoracic parietes, belong distinctly to the lower part of the register because the fundamental tone of the chest wall is one of slow vibration.

Interesting results are obtained on auscultating, both without and with pressure of the stethoscope, the normal chests of persons with good singing voice. When a high or "head" note is voiced and held, the sound as heard through the stethoscope applied to the upper chest is little changed, though it is apt to be made more intense and brought nearer the ear by pressure. Near the base of the lungs, pressure decreases the intensity of the sound, but in neither case is there a marked change in the pitch or quality of the note. On voicing a low or "chest tone," however, pressure applied to the stethoscope produces extraordinary changes in the

[8] Diagnostik der Lungenkrankheiten, Zeitsch. f. ärztliche Fortbildung., 1912, ix, Nr. 14.

sound. With pressure the fundamental tone and apparently the lower partials are damped and the pitch and quality of the transmitted tone are altered and its intensity diminished. It must be borne in mind that it is possible for the thoracic viscera to undergo more or less profound pathological changes without essential modification in their acoustic properties. In such exceptional cases the results of stethoscopic pressure would be negative. Also, although modification from the normal of sounds heard with stethoscopic pressure determines visceral changes with unparalleled delicacy, the specific nature of these changes is not thereby determined; we only apprehend that *something* is the matter.

In previous writings on this subject I have indicated that to successfully damp the vibrations of the chest wall through stethoscopic pressure the physical structure of the stethoscope itself is of fundamental importance. Further study has led to the more definite discrimination of the physical principles involved in the application of "stethoscopic pressure," and briefly to set them forth is the object of this paper.

A solid body laid upon the chest wall takes up and transmits according to its own elastic properties the vibrations emanating from the latter. When the pressure of the solid body upon the surface is sufficiently increased the sensible vibrations of the latter are damped, but their energy is, of course, transferred to the body which extinguished them. When, for example, the uniaural, solid stethoscope is applied to the chest the sounds heard through it are not deadened by increasing the pressure of contact; on the contrary, they tend to become more intense, and are brought nearer the ear.

The same result is obtained with the use of the binaural air-conducting stethoscope, in which the ear and chest pieces are connected by a conducting solid medium, such as a spiral wire. With the simplest form of binaural stethoscope, however, in which the ear and chest pieces are joined by plain rubber tubes, the results of pressure are wholly different. If the bell of such a stethoscope is thick-walled and has a high fundamental tone the damped mural vibrations do not sensibly affect it, and therefore there come to the ear only such vibrations as are transmitted from the viscera of the thorax through the disk of tissue enveloped by the stethoscope bell. If the chest-piece of the stethoscope is thin-walled, and therefore easily set into vibration, or, as in certain popular and excellent instruments, is provided with a disk designed to vibrate, the vibrations set up in the chest piece will not be annulled by pressure, but will be transmitted to the air of the rubber tubes and conducted to the ears.

Our conclusions may be condensed as follows: The sounds heard in auscultation of the chest are compounded of both visceral and mural vibrations, of which the latter, especially in the lower

parts of the musical scale, may greatly preponderate in intensity, but of which the former are alone usually of clinical interest.

The *quasi* adventitious sounds due to sympathetic vibration of the chest wall may be damped and rendered more or less inaudible by firm pressure applied to the bell of the stethoscope. In order to thus annul the sound from mural vibrations the instrument must transmit by pure air conduction, and its chest-piece must not itself sensibly take up the vibrations of the chest wall.

A CLINICAL AND EXPERIMENTAL INVESTIGATION OF THE THERAPEUTIC VALUE OF CAMPHOR.

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The profession has long felt the need of a more accurate knowledge in regard to the relative value of the several drugs employed as so-called "circulatory stimulants." Since this problem first occupied the minds of the writers, important contributions have been made. The present communication appears to be justified, nevertheless, because of the obscurity which still surrounds many members of the group. Thus as concerning the therapeutic value of camphor there has been so far rather more of speculation than of positive knowledge.

A study of some of these drugs was contemplated by us as early as the autumn of 1909. However, the present research was directly stimulated by observation of the following case: In the spring of 1910 a relative of one of us died as the result of a widespread infection, secondary to a suppurative cholecystitis. During the last three weeks of the patient's life there were several periods of alarming circulatory breakdown, occurring during the course of a clinical auricular fibrillation. These acute seizures were apparently due to the action of the infective agents upon the myocardium and vasomotor apparatus. During the attacks, attempts were made to improve the mass movement of blood by the hypodermic administration of such substances as caffein, strychnine, and camphor. The use of camphor was followed in more than one instance by a marked temporary improvement in the character of the pulse and in the general condition of the patient. Nevertheless, the general course of the disease was downward.

On the last day of the patient's life hypodermic medication by camphor was frequently employed in the hope of influencing favorably a gradually failing circulatory apparatus. This treatment was without apparent effect, except that it resulted in annoyance to the patient, and added distress to his family.

A resort to frequent hypodermic injections in the face of an almost hopeless condition had often been observed by us, but it is evident that, to be justifiable, such interference must be expected to result occasionally in benefit to the patient. Any rational confidence in therapy must necessarily be based upon a knowledge of at least the results which may be expected from the exhibition of a remedial agent. Such knowledge was lacking in regard to camphor, the one remedy which had appeared to benefit the above-mentioned patient. Therefore, we decided that our proposed investigation of the cardiac stimulants should be inaugurated by a study of this drug.

The method of bedside study which was subsequently followed by us owed its inspiration to Dr. James MacKenzie, whose brilliant work upon members of the digitalis group has had such a far-reaching effect in stimulating the clinical study of drugs in their action upon the human circulatory apparatus. In addition, coincident laboratory experiments were instituted, the object of which was the determination of the effects of camphor upon the lower animals.

We had for some time shared the belief that the best hope for advance in practical therapeutics lay in the close coöperation of clinical and laboratory workers. To this end, therefore, our bedside and laboratory results on camphor have been frequently compared, and mutually criticised during the course of the ensuing experiments. When the investigation was already well under way the Council of Pharmacy and Chemistry of the American Medical Association formulated its admirable plan of coöperative clinical study of the cardiac stimulants. The proposed method of clinical investigation as recommended by it closely corresponds with that which had been independently adopted by one of us, and which was then being followed in our work with camphor.

The present communication is of a preliminary character, and represents the results obtained thus far in our combined research.

In reading the available literature on camphor one is impressed by the great diversity of opinion as to the mode of action, toxicology, and therapeutic value of the drug. Moreover, reports as to the clinical utility of camphor, although often enthusiastic, are apt to be unconvincing. There is, nevertheless, a widespread belief in camphor as an efficient "heart stimulant." In response to inquiry one may learn that many competent practitioners still rely upon the drug as the best which can be employed in combating a sudden failure in cardiac force, or impairment in vasomotor tone, or both. Moreover, one may find that the hypodermic use of

camphor in oil is frequently resorted to in ambulance work, in the operating room, and at the bedside, in order that an apparently impending circulatory failure may be averted.

Extremely divergent views are held as to the dosage of camphor. Thus, it appears that the customary hypodermic dose in America and England is about 3 grains, whereas in Germany the average dose is much larger. The following references are illustrative.

Hirschfelder[1] says that the average dose of camphor in oil is 2 grains.

Sollman[2] gives the dose as 1 to 5 grains and Cushney[3] as 2 to 10 grains.

Allbutt[4] writes: "Of the larger doses of camphor used by some physicians in heart failure I have no personal experience, and I should be a little timorous of giving it in doses of from 5 to 20 grains as recommended by some authors. Nevertheless, the drug is well spoken of as a cardiac restorative, and much of this testimony is by physicians whose opinion is not to be overlooked."

The issue of the *Therapeutic Gazette* for June 15, 1912,[5] contained an editorial article commenting on the use of camphor. Webster's article[6] was quoted in which that author advocated the employment of the drug in pneumonia in a daily dose of 30 grains. This dose was regarded by the editorial writer as excessive and dangerous, and he stated that he believed that "If 1 or 2 grains fails to do good, then larger doses will not produce beneficial results."

An abstract in the same journal[7] cites several cases of alleged poisoning by this drug; the author, however, admits that poisoning by camphor is rare and generally not fatal. In several instances he admits that the quantity ingested was exceedingly small. Thus one case of fatal poisoning is said to have occurred as the result of eating candy containing camphor, while Blyth is quoted as of the opinion that from 7 to 40 drops of Rubin's spirit of camphor have produced coma, convulsions, and partial paralysis.

Hausemann[8] has collected 30 cases of camphor poisoning principally from the field of the older English literature. He mentions instances in which a few drops of spirit of camphor had caused severe collapse, convulsions, and coma. Further references are made to "self-experiments," in which the ingestion of 2.5 grams of camphor have resulted in cramps and convulsions.

Kobert[9] gives the therapeutic dose as 0.1 to 0.2 gram in oil.

[1] Diseases of the Heart and Aorta, 1910, p. 183.
[2] Text-book of Pharmacology, 1908, p. 465.
[3] Pharmacology and Therapeutics, 1910, p. 73.
[4] Practical Treatment, edited by Musser and Kelly, 1911, ii, 55.
[5] The Use of Camphor as a Diffusible Stimulant, xxxv, 406.
[6] Medical Record, lxxix, 145. [7] Therapeutic Gazette, May 15, 1912, p. 344.
[8] Handb. der ges. Arzneimittellahre, ii, 964, Berlin, 1875; Hausemann und Hilgen, Die Pflanzenstoffe, 2 Aufl., i, 555.
[9] Lehrbuch der Pharmakotherapie (43), 45 Stuttgart, 1897.

The following references support the view that camphor may be used with safety in larger doses than those above mentioned:

v. Leube cited by v. Jaksch,[10] gave 20 grams in a day to a patient with heart failure.

Vogl[11] recommends as many as 4 grams as a dose.

Happich[12] states that from 5 to 15 grams of camphor or from 25 to 75 c.c. of 20 per cent. camphor in oil may be injected subcutaneously in a day.

Schmiedeberg,[13] on the other hand, writes that a man will be surely severely poisoned by taking a dose of 10 to 15 grams, but that a medium-sized dog can eat 30 grams in a day without dangerous symptoms. This author calls attention to the fact that members of the canine family are not affected by the smell of camphor; yet this odor is obnoxious to the cat.

Happich[14] states that the lethal dose by the mouth for the dog varies greatly. From 8 to 20 grams were given without bad results, and one dog received 20 grams a day during a period of ten days without poisoning.

Seibert[15] reports the use of 2.4 grams of camphor in oil injected subcutaneously every twelve hours in the treatment of pneumonia, and states that even 10 c.c. of 30 per cent. camphor in oil causes no poisioning when injected hypodermically every eight to twelve hours.

Webster, during a period of four days, has employed camphor hypodermically in daily doses of 30 grains without the production of untoward symptoms.

Schlutz[16] found that in infants weighing 2400 to 4500 grams, 0.15 to 0.3 gram of camphor could be given by the mouth without the production of dangerous symptoms, but that in cases of malnutrition a relatively smaller dose could cause intoxication.

The above examples suffice to indicate the extreme divergence of opinion among authors as to the safe doses of camphor. While some fear to give more than 2 to 5 grains, others claim that ten times this amount may be administered without bad effect. The explanation of the variation in the results obtained from the administration of camphor may be found in part in the metabolism and excretion of the drug.

Schimiedeberg and Meyer[17] found, as Wiedemann before them had found, that when camphor is absorbed it quickly unites with glycuronic acid and is rendered inert. It is subsequently excreted in the urine as camphoglycuronic acid. However, a

[10] Nothnagel's Spec. Pathologie, 1897, S. 380.
[11] Eulenberg's Realenzyklopadie, Kampfer.
[12] Mittheilungen aus den Hamburgischen Staats-Krankenanstalten, 1908, (8) 1.
[13] Pharmakologie, 1909, S. 274.
[14] Loc. cit.
[15] Medical Record, 1912, p. 743.
[16] Zeitsch. f. Kinderheilkunde, 1911 (1), 197.
[17] Zeitsch. f. physiolog. Chemie, 1907 (3).

variable fragment may escape such combination and be excreted uncombined by the lungs. It is this fragment which is regarded as responsible for the physiologic action of the drug.

Happich found that camphor caused death in emaciated or CO_2 asphyxiated rabbits, whereas glycuronic acid with camphor injected intravenously into such animals caused no intoxication. This authority also remarked that this finding explains why one dog may be killed with 8.5 grams of camphor while another may receive even 20 to 25 grams without injury.

Schlutz[18] believes that in this fact lies the explanation of the toxic symptoms produced by camphor in the poorly nourished infants studied by him. He thinks that in such cases there is probably not enough available glycuronic acid to unite with the camphor, and that the uncombined fragment is accordingly greatly increased in amount. Therefore, intoxication results; whereas, in well-nourished infants there is enough glycuronic acid to unite with nearly all of the camphor, and hence the unchanged fragment is so small that no intoxication occurs even after relatively large doses.

If the foregoing supposition be correct it becomes evident that care should be exercised in the administration of camphor to those patients who have a poor glycuronic acid content. This condition may be suspected in cachexia, in starvation, and in cases of CO_2 poisoning, of severe sepsis, of eclampsia, etc.

It is not the purpose of this communication to deal with the toxicology and action of camphor upon the tissues and organs not directly associated with the circulatory organs. It may, however, be observed that there is good evidence that camphor may act as an excitant on the central nervous system and as an irritant to the gastro-intestinal tract. Small doses, according to Schmiedeberg, induce cerebral symptoms such as dizziness, headache, confusion of ideas, and delirium. With large doses (10 to 15 grams) severe poisoning occurs, evidencing itself by pain in the stomach, hallucinations, and convulsions. However, these symptoms later subside and complete recovery follows.

The evidence in regard to the effect of camphor upon the cardiovascular system is of a contradictory character. The drug is said to cause a periodic increase in blood pressure in the curarized animal, an effect due to its action on the vasomotor centre On the heart, small doses cause an increase in rate and force of beat, due to stimulation of nerve endings and of heart muscle. In larger doses there is a concomitant weakening of heart action. Experimentation upon the dog shows that the intravenous injection of 0.04 to 0.1 gram causes a lowering of blood pressure. (Schmiedeberg.)

On the other hand the work of Roth[19] shows that camphoric

[18] Loc. cit.

[19] Jour. Pharm. and Exper. Therap., 1911, ii, 405.

acid is practically without effect upon the circulation. This author found that early in the experiment there was a small sustained rise in blood pressure following either a large or a small dose, but he observed that later the same dose caused a sustained fall. The heart rate was decreased in all but one instance. Roth attributes these results to salt action, and does not consider camphoric acid itself as a heart stimulant.

Cushney believes that the only result obtainable from therapeutic doses of camphor is a slight dilatation of bloodvessels, a condition due to peripheral action. Sassen[20] claims that after small doses (0.1 to 0.5 gram) the pulse becomes fuller and stronger, while after large doses (0.8 to 2.0 gram) its frequency and fulness are diminished.

It appears to be fairly well established that camphor can restore the heart after poisoning with chloral, muscarine, strychnine, and such other drugs as are thought to depress the irritability of the cardiac muscle.

Böhme[21] found that camphor restored the heart after chloral poisoning.

Harnack and Witowski[22] found that muscarine standstill of the heart is removed by camphor.

V. E. Henderson[23] agrees with Böhme. He found that an interference with rhythm brought on by chloral could be frustrated by camphor.

Maki[24] observed that the low blood pressure caused by chloral poisoning was greatly raised (38 to 80 mm.) by camphor.

Laangard and Maass,[25] using a preparation of dextro, levo, and inactive camphor were not able to demonstrate any action on the normal frog's heart after poisoning the heart with camphor. Hämälämen[26] found that camphor can restore the frog's heart after it has been damaged by chloral according to Bohme's[27] method.

Thus it is evident that the results of laboratory investigation strongly support the view that camphor is antagonistic to the depressing effect upon the heart of chloral, and also of muscarine and strychnine.

There is also some laboratory evidence that camphor may restore coördinate contraction of the heart which has passed into fibrillation.

[20] Vergleichende Untersuchungen über die Wirkung einiger Kampferarten, Inaugural Dissertation, 1909.

[21] Archiv f. exp. Path. u. Pharm., 1905, lii, 346.

[22] Arch f. exp. Path. u. Pharm., 1876, v, 401.

[23] Jour. Pharm. and Exper. Therap., 1911, ii, 153.

[24] Ueber d. Einfl. des Camfers, Caffeines, und Alkaloids auf das Herz, Inagural Dissertation, Strassburg, 1884.

[25] Therap. Monats., 1907, xxi, 513.

[26] Skand. Arch. f. Physiol., 1908, xxi, 64.

[27] Loc. cit.

Seligman[28] found that fibrillation of the cat's heart was promptly relieved by camphor, and also discovered that he could not establish lasting fibrillation of the heart while it was being perfused with camphor. Fibrillation occurred only during the application of electrodes, upon the removal of which the fibrillation ceased.

Kronecker[29] called attention to the difference which he believed to exist between the heart of the cat and that of the dog. He stated that he had studied over two hundred fibrillating hearts of the dog without ever having witnessed a recovery from fibrillation, while in the cat heart, spontaneous recovery from fibrillation is not unusual.

Gley,[30] on the other hand, has found that the heart of a newborn puppy is highly resistant to faradization, so that under ordinary conditions, after the removal of the electrodes, normal rhythmic contractions are resumed.

In planning our bedside study of camphor, we decided to limit the investigation to the effects of the drug, as administered hypodermically, upon the circulatory apparatus of human subjects exhibiting varying conditions of the cardiovascular apparatus. We believe that a clinical study of the effect of a drug upon the circulatory system should include observations on the following conditions: changes in the force, frequency, and rhythm of the heart beat; variations in peripheral resistance; alterations in the volume of the blood. Definite results, if obtained, should be analyzed by eliminating vagus action by atropine, by the study of polygraphic tracings, and by a comparison with results obtained in the laboratory.

For the purpose of the present investigation, camphor was dissolved in oil and administered subcutaneously. The drug was obtained from several sources of supply, and was either dissolved under our direction, or obtained in ampullæ specially prepared for hypodermic use. The administration was by single or multiple subcutaneous or intramuscular injection into patients who could be somewhat arbitrarily divided into the following groups:

A. Patients whose circulatory apparatus was apparently normal.

B. Those whose auricles were in clinical fibrillation (confirmed by polygraphic tracings).

C. One patient (2 observations) with valvular disease but normal rhythm.

D. Patients with unclassified cardiovascular diseases, chiefly, however, affecting the myocardium and vascular coats.

In addition to the above, two control experiments were conducted. Sterile oil was injected into a patient of Group A and into one of Group B. All the subjects but one were adults in a state

[28] Archiv f. exp. Path. u. Pharm., 1905, lii, 333. [29] Zeitschr. f. Biologie, 1896, xvi, 529.
[30] Archiv. de Physiologie, 1891, iii, 735; Soc. de Biologie, 1891, 108.

of nutrition from fair to good. Records of pulse and of systolic and diastolic blood pressure were made at frequent intervals covering a period of forty to two hundred and seventy minutes after the injection of the drug; the usual duration of the observation was about one hundred and twenty minutes. The patients were frequently questioned as to the presence of subjective symptoms which might be attributable to the camphor, but in not a single instance was there obtained any evidence of drug action, with the exception of a complaint of burning at the point of administration. The latter sensation was frequently accompanied by local redness and swelling, which lasted for several hours.

This study was carried on under such circumstances as made an estimation of the volume of the blood impracticable. Polygraphic tracings were taken in several of the fibrillation cases before, during, and after the use of camphor, but in no instance was there observed any alteration in the type of radial or venous pulse as the result of the medication. Blood pressure was estimated by the auscultatory method, a Stanton and a standardized Tycos instrument being employed. The point of disappearance of the second sound was recorded as an admittedly unsatisfactory indication of diastolic pressure. During certain of the experiments it was unfortunately impossible to repress the action of such extraneous influences as mental excitement and muscular action. The atropine test did not appear to be indicated in any experiment. Reference to the table which follows will show the type of subject and dosage employed in each experiment, together with the character of pulse as to rate and rhythm, and the systolic and diastolic blood pressure as recorded before and after the administration of the camphor.

The table given below may be summarized as follows:

1. Controls: Injection of sterile oil containing no camphor. (Class A and B.) A single observation was made upon each of two patients. The following variations were noted during the time of observation: systolic pressure, 13 mm.; diastolic pressure, 10 mm.; pulse rate, 12 beats.

2. Patients with apparently normal circulation: (Class A) five observations. In only one (Experiment 5) was there any distinct change in the circulation. The patient showed, seven minutes after the hypodermic injection of 20 grains of camphor in oil, a fall of about 17 mm. in systolic pressure and 25 mm. in diastolic pressure.

3. Patients with auricular fibrillation and various cardiovascular lesions: (Class B) nine observations. In only three was there any distinct change. In Experiments 2 and 3, one observation each, there was a distinct rise in diastolic pressure, and a slight rise in systolic pressure ten minutes after the administration of camphor. One patient received ten grains and the other twenty grains.

Date.	No.	Condition of patient before administration.								Administration.	Condition after administration.					Summary.
		Sex.	Age.	Weight in kilos.	Group.	Pulse.		Diastolic pressure.	Systolic pressure.	Dose.	Time elapsed, minutes.	Pulse.		Diastolic pressure.	Systolic pressure.	
						Rhythm.	Rate					Rhythm.	Rate			
Oct. 2, 1911	1	M.	16	40.0	D.	Regular	84	70	105	Gr. iv Gr. viij, 150 minutes later	30 30	Regular Regular	82 92	90 68	105 112	S. P., rise of 7 and 10 mm. in 15 and 20 minutes respectively after injection. D. P., rise of 20 and 15 mm. in 30 and 10 minutes respectively after injection. Pulse, initial fall of 8 in first 15 minutes; then progressively increased throughout experiment.
Oct. 4, 1911	2	M.	Circa 30	66.8	B.	Very irregular	72	70	130	Gr. x	10	Very irregular	84	110	120	Rise in S. P., D. P., and Pulse in first 10 minutes. All reached starting level at end of experiment (40 minutes).
Oct. 6, 1911	3 Same patient as No. 2	M.	Circa 30	66.8	B.	Grossly irregular	65	90	132	Gr. xx	10	Grossly irregular	70	125	150	S. P., sustained rise of 8 to 18 mm. throughout experiment. D. P., initial rise of 35 mm.; sustained average of 25 mm. Pulse, rise of 15 beats 40 minutes after injection; 20 starting level in 1 hour.
Oct. 10, 1911	4	M.	45	?	Broken compensation C.	Regular	90	99	130	Gr. xx	20	Regular	92	120	132	S. P., negative. D. P., rise of 21 mm.; not sustained. Pulse, rise of 14 to 22, 30 and 60 minutes respectively after injection.
Oct. 12, 1911	5	M.	37	80.0	A.	Regular	68	115	132	Gr. xx	10	Regular	68	90	122	S. P., initial fall of 17 mm.; sustained fall of 7 to 17 mm. for 1 hour. D. P., initial fall of 25 mm.; sustained fall of 10 to 20 mm. for 1 hour. Pulse negative.
Oct. 23, 1911	6 Same patient as No. 4	M.	45	?	Compensation nearly restored C.	Regular	80	80	95	Grs. xx Gr. x, 25 minutes later	10 15	Regular Regular	78 70	80 77	97 97	S. P., negative. D. P., negative. Pulse, negative. Compare results C, No. 4.
Nov. 2, 1911	7	M.	70	90.0	B.	Marked arrhythmia	74	..	215	Gr. xij	55	Marked arrhythmia	70	..	260	S. P., during 55 minutes rise of 45 mm. Marked psychic agitation during experiment. Pulse, unaffected.

Date.	No.	Condition of patient before administration.								Administration.	Condition after administration.				Summary.
		Sex.	Age.	Weight in kilos.	Group.	Pulse.		Diastolic pressure.	Systolic pressure.	Dose.	Time elapsed, minutes.	Pulse.		Diastolic pressure.	Systolic pressure.	
						Rhythm.	Rate					Rhythm.	Rate			
Nov. ?, 1911	8	F.	70	50.0	B.	Grossly irregular	66	160	215	Grs. iij	15	Very irregular	68	150	220	S. P., fell 10 mm. during experiment.
										Gr. iij, 20 minutes later	15	Very irregular	68	170	210	D. P., rise after first and second injection; fall after third.
										Gr iij, 30 minutes after second dose	10	Very irregular	64	155	210	Pulse, probably unaffected.
Nov. 7, 1911	9	F.	36	48.0	Aortic stenosis and insufficiency B.	Marked arrhythmia	66	98	118	Gr. v	20	Very irregular	72	105	122	Negative.
										Gr. v, 30 minutes later	15	Very irregular	70	100	115	
										Gr. v, 30 minutes after second dose.	15	Very irregular	70	103	116	
Nov. 15, 1911	10	F.	64	68.0	A.	Regular	78	95	140	Gr. xv	40	Regular	72	105	130	S. P., fell 14 mm. after first injection; after second injection no effect. D. P., progressive rise of 17 mm. first hour after second injection. Rise, 5 mm. Pulse, gradually slowed 1 beat.
										Gr. x, 55 minutes later	30	Regular	68	115	133	
Dec. 14, 1911	11	M.	42	73.0	A.	Regular	92	94	130	Gr. xv	30	Regular	90	92	117	S. P., fall of 13 mm. after first injection; second injection, no effect. D. P., unaffected. Pulse, unaffected.
										Gr. x, 45 minutes later	15	Regular	92	94	122	
Dec. ?, 1911	12	F.	25	50.0	D.	Regular	64	76	98	Gr. xx	25	Regular	76	70	102	S. P., negative; D. P., negative. Pulse, unaffected.
										Gr. x, 45 minutes later	15	Regular	72	76	98	
Dec. 23, 1911	13	M.	20	70.45	A.	Regular	72	80	127	Gr. xx	50	Regular	74	84	117	Results negative.
Jan. ?, 1912	14	M.	34	54.0	D.	Regular	90	80	140	Gr. xx	25	Regular	84	80	125	S. P., first injection, fall of 15 mm.; second injection, no effect. D. P., negative after both injections. Pulse, gradual fall of 16 beats throughout experiment.
										Gr. x, 40 minutes later	30	Regular	78	85	125	
Jan. 6, 1912	15	M.	38	60.0	A.	Regular	55	70	107	Gr. xx	45	Regular	62	60	112	S. P., no effect. D. P., no effect. Results negative during 40 minutes previous to administration of drug. S. P. rose 7 mm. and D. P. rose 10 mm. Pulse rose 5, 10 minutes after first injection; dropped 5, 10 minutes after second injection.
										Gr. x, 65 minutes later	30	Regular	54	75	112	

Date.	No.	Condition of patient before administration.							Administration.	Condition after administration.				Summary.
		Sex.	Age.	Weight in kilos.	Group.	Pulse.		Diastolic pressure.	Systolic pressure.	Dose.	Time elapsed, minutes.	Pulse.		Diastolic pressure.	Systolic pressure.	
						Rhythm.	Rate					Rhythm.	Rate			
Jan. 24, 1912	16	M.	58	52.0	D.	Regular	72	60	110	Gr. v	25	Regular	70	65	110	Results negative, including respiration.
										Gr. xv, 10 minutes later	15	Regular	68	65	110	
										Gr. x, 40 minutes later						
Jan. 30, 1912	17	F.	37	55.0	Decompensation B.	Grossly irregular	84	60	105	Gr. xx	40	Grossly irregular	80	65	130	S. P., rise of 37 mm. (?) during experiment. Persistent pressure over 130 suggests error in first reading. This patient developed auricular fibrillation while in hospital.
Apr. ?, 1912	18	F.	70	48.0	Marked decompensation B	Very irregular	118	170	215	Gr. ix	30	Very irregular	120	180	225	S. P., fall of 10 mm. before injection. Rise of 10 mm. and fall of 5 mm. after injection. D. P., rise after first injection and fall to starting level after second injection. Pulse not affected.
										Gr. vj, 55 minutes later	20	Very irregular	120	175	220	
Apr. 19 1912	19 Same patient as No. 7	M.	70	90.0	Marked decompensation B.	Very irreglar	80	120	216	6 c.c. sterile oil	15	Very irregular	80	116	220	Control experiment; S. P., preliminary rise of 7 mm. D. P., no fluctuations. Pulse same as after camphor; see next experiment.
Apr. 19, 1912	20 Same patient	M.	70	90.0	Marked decompensation B.	Very irregular	86	120	220	Gr. ix	30	Very irregular	82	120	222	S. P., rise but 3 mm. higher than after plain oil. D. P. and Pulse unchanged. Test for glycuronic acid negative in subsequent 24 hours' specimen of urine.
Apr. 30, 1912	21	M.	36	67.0	A.	Regular	70	83	100	10 c.c. sterile oil	30	Regular	68	75	95	S. P., variation of 13 mm. during experiment. D. P., variation of 10 mm. during experiment. Pulse, variation of 12 beats during experiment.
										7 c.c. sterile oil, 40 minutes later	30	Regular	60	85	89	
Apr. 30, 1912	22	M.	67	76.8	B.	Grossly irregular	100	90	110	Gr. xxx	30	Grossly irregular	96	92	106	S. P., variation of 8 mm. 50 gr. camphor. D. P., variation of 5 mm. Pulse, variation of 8 beats. Contrast C, Experiment 21.
										Gr. xx, 40 minutes later	30	Grossly irregular	104	90	106	

In Experiment No. 7 there was a rise in systolic pressure of 45 mm. during the first fifty-five minutes following the injections of the drug. The patient was a senile dement and became much excited by the proceedings incident to the experiment. A second observation upon the same patient (Experiment No. 20), under apparently like conditions of decompensation, but with less mental agitation and with a slightly smaller dose of camphor, was negative as to result. In Experiment No. 17, in which the injection of camphor was followed by no result, a subsequent use of strophanthin intravenously during a period of acute dilatation exercised a pronounced effect in slowing the rate and improving the condition of the circulation. In no instance was there any effect upon the fibrillation.

4. Patient with valvular lesions and normal rhythm (Class C). Two observation were made upon one patient. In one observation (Experiment No. 4) there were two sharp accelerations of pulse rate, with a quick return to normal, together with an initial rise in the diastolic pressure which was not sustained. No other changes occurred. Experiment No. 6 was negative.

5. Patients with unclassified affections chiefly myocardial. (Class D): Four patients were considered, with conditions of the cardiovascular apparatus not included in Groups B and C. One observation was made in each of four patients. In two of these experiments, Nos. 1 and 14, more or less fluctuation within narrow limits of both blood pressure and pulse rate was found, but in each instance there was a quick return of blood pressure to the normal. The pulse rate in No. 1 rose fourteen beats, while that in No. 14 fell sixteen beats during the respective experiments.

The laboratory investigations consisted in (1) manometric blood pressure observations upon the unanesthetized animal, using the T-cannula method devised by one of us.[31] Normal animals were taken as subjects, except in one instance where camphor was administered in large doses to a moribund animal. (2) Perfusion experiments were made upon the isolated heart of the cat.

The laboratory results were in agreement with the clinical findings. Doses of sufficient size to produce slight muscular twitchings failed to cause any distinct rise in blood pressure, or any increase in rate or amplitude of the heart beat in the normal dog. In the moribund dog (one experiment) there was slight transitory heightening of blood pressure together with increased amplitude and rate of heart beat, coincident with mild convulsive seizures, which possibly contributed to the circulatory changes.

The perfusion of the isolated heart of the cat with a saturated solution of camphor in defibrinated blood and 0.9 per cent. sodium

[31] Heart, 1910, ii, 5.

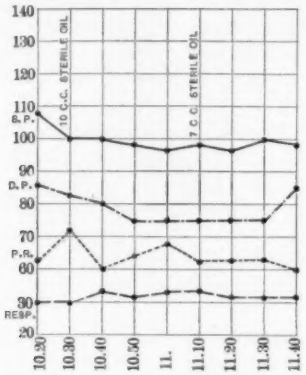

CHART 1.—Observation No. 21. Patient with apparently normal cardiovascular system "control."

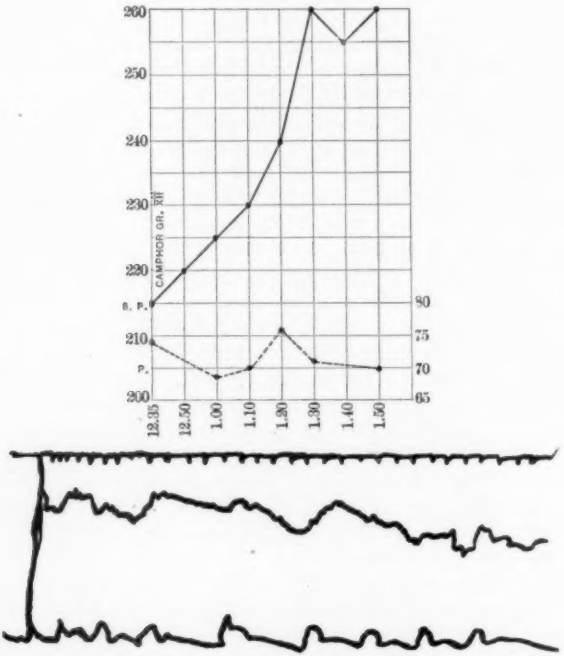

CHART 2.—Observation No. 7. Patient with cardiovascular renal disease; auricle in fibrillation. Many ventricular systoles fail to reach radials. Marked decompensation. Senile dementia. During progress of experiment the patient was greatly excited. There was much voluntary muscular movement, which could not be controlled by the observer. Satisfactory venous tracings were not secured from this patient, as it was impossible to induce him to suspend breathing, while, further, the head was kept in almost constant motion during the attempt.

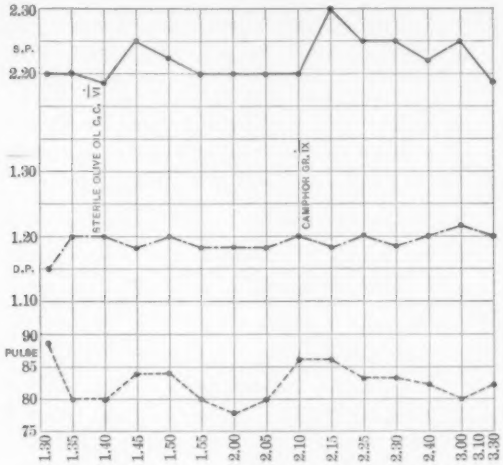

CHART 3.—Observation Nos. 19 and 20. Same patient as in observation No. 7. Condition of patient unchanged as regards fibrillation and decompensation, but as patient was now familiar with the proceeding, there was less mental excitement and muscular movement than was present during the progress of the former experiment.

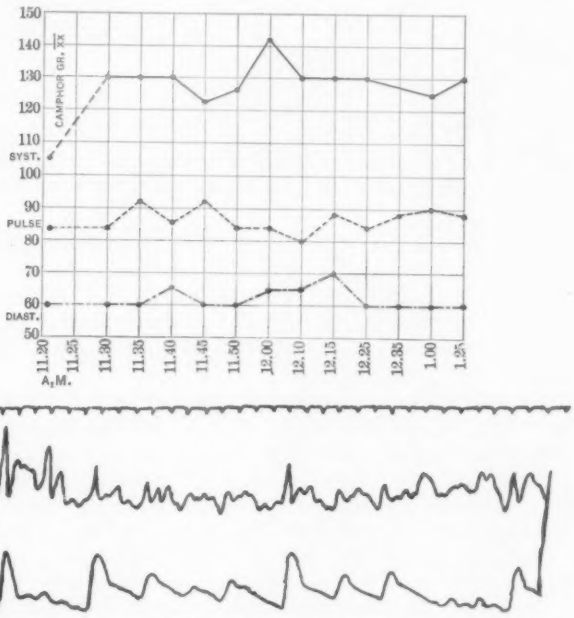

CHART 4.—Observation No. 17. Patient with auricular fibrillation, mitral stenosis, and dilated heart. Patient under the influence of digitalis. Compensation.

chloride solution was without effect upon the normal strongly beating heart. In two instances the fibrillating heart was restored to normal coördinate contractions by perfusion with camphor. The camphor solution employed was, however, a saturated one, and therefore these positive laboratory results should not be interpreted as being in conflict with our negative clinical findings in auricular fibrillation.

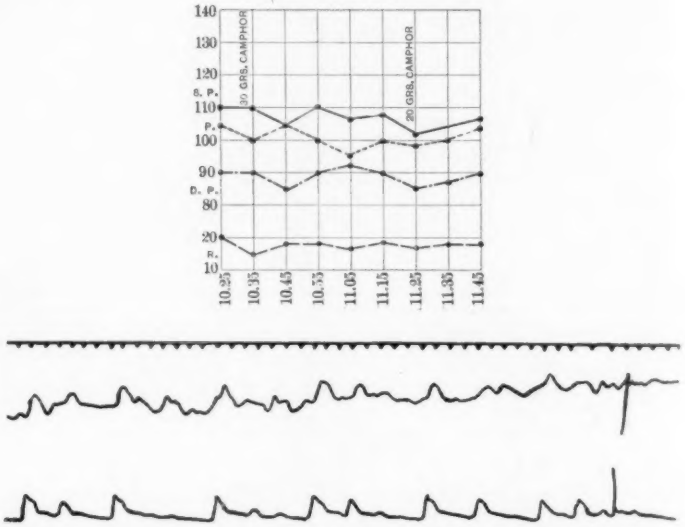

CHART 5.—Observation No. 22. Patient with auricular fibrillation. Compensation. Digitalis.

SUMMARY. In the clinical experiments, camphor injected subcutaneously in oil in doses as large as 50 grains failed to produce any definite effects. The variations in pulse and in blood pressure occasionally following the use of the drug were so inconstant as to make it probable that they had no relation to the medication employed.

The failure of the drug to influence clinical fibrillation of the auricle in the human subject is only in apparent contradiction with our own and other laboratory observations, that perfusion of the isolated cat's heart with camphor may remove fibrillation and restore coördinate contractions. The explanation of this apparent discrepancy is probably to be found in the fact that the dose was greater in the perfusion experiments than was possible in the clinical observations, and that in the former, the condition of fibrillation in the normal heart was induced artificially. A further point to be considered is that different animal species and

varying ages even of the same species show marked differences with respect to fibillation.

In the single laboratory experiment in which a stimulating effect upon the circulation was observed, the positive result was possibly due to the fact that the animal was emaciated and moribund, and that therefore it may not have been possessed of sufficient glycuronic acid to combine with the camphor.

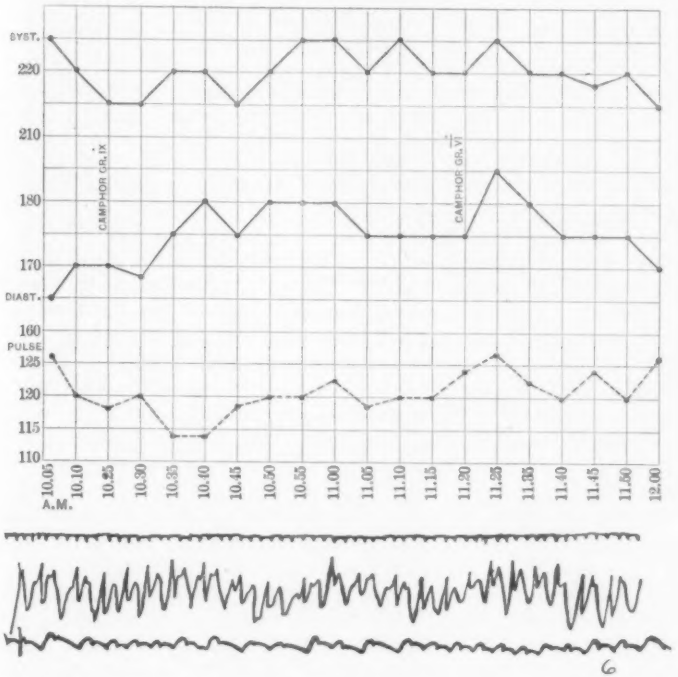

CHART 6.—Observation No. 18. Patient with auricular fibrillation. Marked decompensation. Not under the influence of digitalis.

Therefore, while camphor may be an active agent in certain disorders in which there is an abnormally small glycuronic acid content, and while experiments indicate that the drug exercises a favorable effect upon the heart muscle which is poisoned by chloral, muscarine, or strychnine, nevertheless camphor should neither be relied upon as a cardiac stimulant nor feared as a toxic agent in the doses employed by us and under the conditions studied.

SOME INTERESTING RESULTS WITH THE PHENOLSULPHONEPHTHALEIN TEST.

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In the last few years much interest has been directed by the work of Rowntree and Geraghty[1] to the phenolsulphonephthalein test as a means of determining the functional efficiency of the kidneys. As a rule, both in clinical and experimental work,[2] a close correlation has been found between the impairment in the elimination of the dye and the degree of nephritis, as indicated by clinical symptoms, other laboratory tests, or autopsy findings. Rowntree and Geraghty, however, state that in the study of 25 cases of chronic parenchymatous nephritis they found 5 mild cases of short duration, with only slight edema, which showed a normal excretion of the dye. In cases of longer standing, or cases in which the disease was of ordinary severity, the time of appearance of the drug was always delayed, and the amount excreted was definitely below normal.

The following report of a boy, aged nineteen years, who was admitted to the medical wards of the University Hospital in May, 1912, is of interest because of unusually good phthalein elimination in spite of the existence of a parenchymatous nephritis, with marked epithelial degeneration, and of definite impairment in one of the renal functions, that of chloride elimination. The chief proof of the existence of an anatomical nephritis in this patient is found in the urinary examinations. The urine in twenty-five examinations over a period of three months during which the boy was under observation never failed to show a large amount of albumin, which, estimated by the Esbach method, varied from 2.7 to 8 grams per liter; at the same time an exceedingly large number of hyaline, granular, fatty and epithelial casts, free-fat droplets, and much renal epithelium containing fat droplets were constantly found in the urinary sediment. Ureteral catheterization on July 15, recovered urine with these characteristics from

[1] The Phthalein Test, Arch. Int. Med., 1912, ix, 284.

[2] J. H. Austin and A. B. Eisenbrey, Experimental Acute Nephritis: The Elimination of Nitrogen and Chlorides Compared with that of Phenolsulphonephthalein, Jour. Exper. Med., 1911, xiv, 366.

each ureter, thus excluding a unilateral lesion. Such a series of urinary findings can scarcely be explained on any basis other than that of a parenchymatous degeneration of the renal epithelium. Additional evidence of nephritis was the presence of a moderate edema of twelve weeks' duration, and, as will be shown later, a slight impairment in chloride tolerance. The etiology of the nephritis has not been discovered.

The complete physical examination revealed slight edema and cyanosis of the extremities, moderate enlargement of the liver, the heart slightly enlarged to the right, and typical auscultatory findings of a moderate mitral stenosis. Within a few days after admission the enlargement of the liver disappeared, as did also the cyanosis of the extremities; the edema diminished, but has never entirely disappeared. The urinary findings two and a half months after the disappearance of all signs of circulatory insufficiency were practically unchanged.

Table I gives the results of the routine urinary examination:

TABLE I.

Date.	Amount.	Specific gravity.	Reaction.	Albumin, grams per liter.	Hyaline casts.	Granular casts.	Fatty casts.	Epithelial casts.	Cylindroids.	Red blood corpuscles.	Epithelial cells.	Free fat.
July 1	....	1025	Alk.	4	Many	Many	Many	...	+	Few	+	+
July 7	....	1019	Acid	Cloud	+	Many	Many	...	0	0	Few	+
July 9	970	1019	Acid	3	+	+	+	+				
July 15	790	....	....	5	...	Many	Many					
July 27	1350	1012	Acid	2.7	Many	Many	Many					
Aug. 7	1600	....	....	3	Many	Many	Many	Many	....	....	....	+
Aug. 15	....	1007	Acid	Cloud	...	Few	...	...	Few	Few	Few	
Aug. 16	....	....	....	Cloud	Many	Many	Many	Many	....	Few	....	+
Aug. 27	....	1013	Acid	Cloud	...	Many	...	...	Few	Few		
Aug. 30	2170	1011	....	2.5	...	Many	Many	...	Few			
Sept. 10	....	1017	Acid	3.7	Many	Many	...	...	Few	Few		
Sept. 30	....	....	Acid	Cloud	Many	Many	...	...	....	Few		
Oct. 3	1600	1013	Acid	4	Many	Many	...	....	....	Few		
Oct. 6	1030	1019	Acid	5	Many	Many	Many	Many				

In view of the evidence of definite nephritis, studies of the functional efficiency of the kidneys were instituted. The phthalein test was twice performed according to the technique of Rowntree and Geraghty. The following surprising results were obtained:

July 5. Elimination after one hour, 50 per cent.; after two hours, 71 per cent.

September 14. Elimination after one hour, 67 per cent.; after two hours, 82 per cent.

The indigo-carmine test was done on July 15, and the dye was seen coming from each ureteral orifice at the end of six and one-fourth minutes. Both of these functional tests showed, therefore, unusually prompt elimination.

Studies were then made of the chloride and nitrogen elimination

after the addition of known quantities of sodium chloride and of urea to a constant diet. The patient was put on a salt-poor soft diet, with constant quantity of milk and 7 grams of sodium chloride every twenty-four hours, beginning September 16; the sodium chloride was increased and urea added to the diet as indicated in Table II. The total elimination or chlorides was estimated by the Volhard-Arnold method, and of nitrogen by the Kjeldahl method. (See Table II.)

TABLE II.

Twenty-four hours beginning	Amount of urine in c.c.	Specific gravity.	Albumin by Esbach. Grams per liter.	NaCl added to food.	NaCl in urine.	Nitrogen in urine.
Sept. 19	1520	1.013	6	7 grams	7.9	
Sept. 20	1220	1.013	7	7 grams	6.8	
Sept. 21	1100	1.016	7	7 grams	7.3	
Sept. 22	1520	1.016	6.5	10 grams	10.03	
Sept. 23	1380	1.015	6	20 grams	13.1	11.35
Sept. 24	1530	1.014	5.5	20 grams	16.9	11.85
Sept. 25	1375	1.015	7	7 grams	14.3	11.8
Sept. 26	1500	1.017	8	7 grams	12.6	15.0 Given 10 grams urea by mouth = 4 grams N.
Sept. 27	1350	1.018	7.5	7 grams	12.1	12.1
Sept. 28	1540	1.014	6	.....	8.3	9.4

These results show no delay in the nitrogen elimination and fair elimination of sodium chloride. There is, however, some delay in the elimination of the larger amount of sodium chloride given, and this, together with an increase of edema on the days of high chloride administration, which promptly subsided during the next few days, is suggestive of beginning impairment in the chloride tolerance. It is not to be understood that the patient was on a perfect salt balance in this experiment.

Although recent work would indicate that the phthalein test is the most reliable single test of renal efficiency, we have apparently occasional cases of nephritis, as that presented, in which beginning impairment in the chloride-eliminating capacity of the kidney is evident at a time when the phthalein elimination is still unusually prompt.

A second case that seems worthy of mention gives the following history: At the age of six years the patient, a male, had an attack of scarlet fever followed by edema. Good health returned and continued for ten years, until, at the age of sixteen, he developed an abscess in the left iliac fossa. This was opened and drained. Following the operation general anasarca of a severe grade developed, and a fatal termination seemed imminent. A bilateral decapsulation of the kidneys was followed by improvement, and the patient left the hospital in good condition four months later.

His health has been good for three years since, except for short periods of renal inadequacy every four to eight months. At these times he exhibits edema and some decrease in the amount of urine. He recently returned to the hospital in one of these attacks. Examination of the urine showed 2 grams of albumin per liter, many and various casts, and some blood. However, after but a few days of treatment, with improvement, his phenolsulphonephthalein elimination was 46 per cent. in the first hour and 23 per cent. in the second hour, a total of 69 per cent., or approximately normal. Here again the phenolsulphonephthalein elimination cannot be considered a true index of the health and efficiency of the kidneys.

The third case of interest was one of bilateral polycystic kidneys. The patient, a man, aged forty-two years, under observation for two weeks previous to death, had been in good health until about a month before admission. He then began to suffer with pain in the lumbar region and hematuria associated later with vomiting and other symptoms of uremia. He was admitted to the hospital in September, 1912, and at this time presented evidence of an infection, that is, a septic temperature running as high as 103°, with occasional chills. The amount of urine passed was fairly abundant, ranging from 800 c.c. to 1000 c.c. per day. Urinalysis at first revealed a low specific gravity, little albumin, and no formed elements, later the albumin increased and many hyaline and light granular casts appeared, with finally numerous erythrocytes.

The phenolsulphonephthalein test was performed twice, thirteen and eleven days before death. At each test the elimination in two hours was an unmeasurable trace, though the elimination of the dye in traces continued for about eight hours. Up to the last day before death the elimination of water by the kidneys was quite free and the chlorides and nitrogen of a restricted diet were approximately completely eliminated. Accurate metabolic studies could not be made because of vomiting, but the elimination in the urine in twenty-four hours was for several successive days from 2.64 to 4.3 grams of sodium chloride and 4.4 to 5 grams of nitrogen. The development of uremic symptoms steadily progressed, ending in death. At autopsy the clinical diagnosis was confirmed by the finding of large polycystic kidneys, in which almost no renal tissue could be found. The symptoms of infection were explained by a suppurative process in the bile passages, associated with gallstones and multiple abscesses of the liver. It is of interest that small cysts were found throughout the liver, a finding probably to be correlated with the polycystic kidneys.

Rowntree and Geraghty make note of a patient with hypertrophied prostrate and normal phthalein elimination who died later of pneumonia, and at autopsy was found to have bilateral

polycystic kidneys. The phthalein test, however, showed no evidence of renal insufficiency.

These two findings in polycystic kidneys tally with the clinical picture in this disease, renal function being apparently adequate for years until some intercurrent infection causes impairment, and eventually uremia and death.

Rowntree's case of polycystic kidney is an example of good elimination before, and ours of faulty elimination after, the intercurrent infection.

This brief report is presented for the purpose of calling attention to certain interesting phases of phthalein elimination, and with no intention of minimizing the importance of the test, which, on the contrary, we believe to be of the greatest value for the determination of renal efficiency.

PRIMARY ADENOMATA OF THE LIVER SIMULATING HANOT'S HYPERTROPHIC LIVER CIRRHOSIS.

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Adenomata of the liver are rare, and only the most meager mention of these tumors can be found in our recent text-books or systems of medicine, or even in our standard works on pathology. From the literature we have been able to collect but 44 cases of this condition, 16 of which were solitary, and 28 multiple. Of the latter 28 there were 21 associated with the atrophic cirrhosis of Laennec and the remaining 7 had no mention of any cirrhosis whatever. These primary cases were accidental discoveries at autopsy, and no reference was made to any symptoms which they may have induced. In 25 of the 44 cases the tumors were composed of modified liver parenchyma, and in 19 the structure was that of agglomerations of large bile ducts. Of these 19 there were 4 multiple and 15 solitary.

The greater portion of these cases were unaccompanied by any sort of clinical history, and were apparently collated for the sole purpose of the statistics of incidence.

In his book *Diseases of the Liver*, Rolleston devotes some space

to the consideration of adenoma of this organ. He divides all adenomata into three classes: (1) Composed of or derived from the ordinary parenchymal cells; (2) those derived from the bile ducts; (3) those due to the inclusions of adrenal "rests." Since the case herewith reported comes under the first class we will confine our attention to it alone.

In common with all who refer to the condition at all, Rolleston holds that the majority of instances of multiple liver adenomata are associated with and secondary to cirrhosis of that organ, the condition being essentially a compensatory process of cell hypertrophy to offset the destruction of the parenchyma by the disease. He regards them as "exaggerations of the hobnails seen in portal cirrhosis," and states that they are to be explained as a final stage of this nodular hyperplasia. Necrosis, fatty metamorphosis, and portal thrombosis are particularly apt to follow. On the other hand, Engelhardt ascribes their etiology to a toxin which has been producing the connective-tissue hyperplasia of the cirrhosis and is supported later in this view by Dieulafoy. The toxins of malaria have been known to produce adenoma of the liver, and injections of toxins resulting from blastomycetic infections have produced the same result. In favor of the compensation theory, it may be mentioned that in the portal cirrhoses where the cell destruction is most marked the majority of instances of adenoma occur, while in the types of cirrhosis which are characterized by long preservation of the liver cells it never occurs.

A very common fate of adenoma of the liver is their malignant transformation into carcinomata, according to Sabourin, who has written extensively on this phase of the subject. This is usually fairly early in the history of the adenomatous condition, and is nearly always accompanied by infiltration of the portal vessels, with consequent tumor-cell emboli, by spread to the other surrounding structures, and by metastasis to various tissues by way of the lymphatics.

According to Rolleston and emphasized by Engelhardt, in nearly all of the cases of multiple adenomata there is associated with the cirrhosis a thrombosis of the portal vein, and consequently a high percentage of these tumors are marked by the vomiting of blood and by ascites.

Many of the foregoing data are of interest in the light of the case here reported, and are, therefore, selected for mention.

Case History.—The patient, C. M. H., aged thirty-one years; married; occupation, paper-box manufacturer. First consulted one of us on May 31, 1906, complaining of weakness, loss of appetite, pain, dragging in the abdomen, and jaundice.

He has had all the infections of childhood, since which time he has been in perfect health until about two years ago, when he developed what was then diagnosticated as a severe attack of

influenza. He dates his present illness from that attack, never having been well since. He denies all venereal disease. He has never been in the tropics, and has never suffered from malaria or dysentery. His habits are of the best. He uses no tobacco or alcoholic stimulants. He complains of weakness, dragging, and fulness of the abdomen, dull pain in the back and loins, and loss of appetite. He states that he has had several attacks of feverishness for which he could not account. He has never bled from the gums, nose, stomach, or rectum. He never suffers from headache, and his bowels are regular. The stools, he states, are light yellow in color, and he has never observed them clay colored. His urine is abundant, dark in color, and deposits much brick-dust sediment. He has noticed that the jaundice from which he suffers fluctuates in intensity. Sometimes his skin is extremely dark and at other times much bleached.

EXAMINATION. The patient is a well-built man, his muscles are flabby, and the visible mucous surfaces are pale. His skin and conjunctivæ are universally and deeply bile-stained. There is no edema or cyanosis. His respirations are quiet and the pulse slow. The skin is dry and a little harsh.

Lungs: Apart from a moderate degree of emphysema they seem normal.

Heart and Arteries: The cardiac impulse is visible in the fifth interspace 8 cm. to the left of the midsternum. No friction or thrill over the precordium exists. The cardiac dulness is nearly effaced by a hyper-resonant note. There is a soft basic systolic murmur slightly conducted into the carotids and also heard over the pulmonic and aortic interspaces. A soft systolic apical murmur is heard, conducted feebly to the left. The pulse is 60, regular, soft, and easily compressed. The systolic blood pressure is 130 mm. of mercury; the diastolic pressure, 80 mm.

Blood: Red cells, 3,250,000; white cells, 8000; hemoglobin, 70 per cent.; color index, 1. The red cells presented no nucleated forms and no poikilocytosis. No malarial parasites seen. The staining reaction was good.

Abdomen: The whole upper half of the abdomen is full and prominent. There is a slight right inguinal hernia, easily reducible. There are no enlarged veins traversing the abdomen or chest; no dulness exists in either loin or in the dependent parts of the abdomen when standing. The kidneys are not palpable.

Liver: The dulness of the right lobe of the liver in the midclavicular line extends downward from the level of the fifth rib 18 cm., while that of the left lobe extends downward from the sternoxiphoid articulation 20 cm. The liver border is rounded, firm in consistency, painless on pressure, and has no palpable nodules. A deep notch, easily palpable, separates the large and heavy left lobe from the right. Another deep notch exists in the

position of the fissure of the gall-bladder. The latter organ, however, is not palpable.

Spleen: The dulness of the spleen extends from the seventh rib downward and forward, whence it apparently blends with the dulness of the left lobe of the liver. Its lower border is firm and smooth.

Rectum: Examination of the rectum showed no hemorrhoids. The prostate gland was normal in size and consistency and perfectly smooth.

Glands: No enlarged lymph glands were detectable. There was no joint or bone tenderness.

Nervous System: Examination of the nervous system was entirely negative. The ophthalmoscope showed no changes in the optic disks or retinæ.

Urine: Twenty-four-hour specimen; amount, 3 pints. Reaction, acid; color, dark amber; specific gravity, 1022; foam, bile-stained. All tests for bile, positive. No albumin or sugar; no indican. There are a few bile-stained casts. No blood cells discernible. Amorphous urates in abundance.

The stool was light yellow in color and soft in consistency. It contained no mucus, amebæ, blood, or other pathogenic parasites.

He was again examined in April, 1907, and the following notes taken:

Jaundice much more intense. Slight soft edema about the tibiæ, no cyanosis, slight general emaciation. The left lobe of the liver almost fills the upper half of the abdomen, extending downward two fingers' breadth below the umbilicus. The right lobe, though very large, appears much like an appendage to the left. The spleen, owing to the large left lobe of the liver, is palpated with difficulty. No enlarged veins are visible and no signs of free fluid exist in the peritoneal cavity. No hemorrhoids are present. Systolic, basic, and apical murmurs are present. The systolic blood pressure is 120 mm. of mercury. The blood picture is that of a secondary anemia. The stools are light though not clay colored. The patient states that the stools change their color from time to time. Physically, he is much weaker, has a fickle appetite, and suffers from great itching of the skin and from insomnia.

He was observed from time to time during the year 1907, but no remarkable change in his condition was found. His jaundice would fluctuate; at times he would become dark and again much lighter. His stools, while not clay-colored, were much lighter than when he first came under observation. He resided in the country and remained in fair health until the fall of 1908, when all his symptoms became much worse: his jaundice was intense, his stools about clay-colored, his urine scanty and full of bile, his gums vascular and bleeding on the slightest provocation, but without hemorrhage from any other mucous surface. His liver remained about as described above,

the left lobe always being the most prominent. There was no evidence of portal obstruction. A week before his death, however, changeable dulness was detected in each flank, but not enough fluid existed to produce a fluctuation wave. A few days prior to death he became delirious, drowsy, gradually passed into deep coma, which lasted about forty-eight hours, and died.

The complex of symptoms presented during the course of the disease were: (1) A long, continuous jaundice fluctuating in intensity; (2) a gradual but progressive liver enlargement until it became of enormous size, with special prominence of the left lobe; (3) definite though moderate enlargement of the spleen; (4) absence of acholic stools until within a few days of death; (5) absence of ascites, hemorrhages from mucous surfaces, or enlargement of the abdominal or hemorrhoidal veins; (6) presence of attacks of abdominal pain, with febrile reaction; (7) abundant bile-stained urine; (8) cholemia and death.

The presence of the above complex naturally led to a diagnosis of hypertrophic biliary cirrhosis of the type of Hanot. Owing to a moderately well-developed panniculus, and also to the fact that most of the tumor masses located on the ventral wall were small, the nodules were not palpable.

Autopsy. Mr. C. M. H. Performed by Dr. H. W. Carey, March 8, 1908. Autopsy No. 105, from the Samaritan Hospital records.

The body is that of a well-nourished man, 170 cm. in length. There is marked jaundice of universal distribution, together with much staining of the conjunctivæ. The pupils are equal. The abdomen is slightly distended and full in the flanks. There is slight edema of both ankles. Rigor mortis is well marked. There are no enlargements of the superficial lymph glands. The superficial veins are not enlarged. The body has been embalmed.

The peritoneal surfaces are normal save for a line of adhesions along the course of the urachus to the coils of the intestines above the pubes. It contains no dilated veins. The appendix is normal. The coils of intestines are normal.

On raising the costal flap no enlargement of the internal mammary veins is noted.

The lungs are normal except for two small infarcts on the lower border of the right lower lobe. There is slight edema and congestion of the lower lobes of both.

The bronchial glands are normal.

The pericardial sac is normal.

The heart shows considerable thickening of the aortic valve, due to vegetations on the proximal side of the leaflets, which narrows the valvular orifice and renders the valve as a whole, incompetent.

The spleen is about normal in size and weighs 645 grams. It is

negative throughout. Nearby in the omentum are two small accessory spleens about 1 cm. in diameter, but presenting nothing unusual in their structure.

The stomach is normal.

The pancreas is normal.

The kidneys are normal save for a marked pallor and indistinct markings in the right.

The adrenals are normal. There are no signs of tumor growth seen.

The intestines, bladder, genitalia, and bone-marrow are normal.

The liver: On opening the abdomen the lower border of the liver presents in the midline 11 cm. below the tip of the ensiform cartilage. On removing the chest wall the portion first visible is seen to be the left lobe, the right lobe being pushed well into the right flank and encroaching above upon the right pleural cavity. On removal of the liver it is found to weigh 2445 grams (5.3 pounds).

In color, the liver is nearly all of a peculiar yellowish green, but a small portion is fairly normal purplish red. The whole surface is broken up into literally innumerable nodules, leaving no part of the surface smooth. Over the upper surface these are approximately 1 mm. to 1 cm. in diameter, while on the under surface most of them are much larger, measuring from 2 cm. to 3 cm. These nodules, where not bile-stained, are dark purplish red and do not show the light yellowish or bleached appearance common to fatty deposits in nodular livers. The interstices between the nodules are not rich in fibrous tissue nor are the depressions so sharp as in the surfaces of atrophic cirrhosis. In some places the capsule is thickened, but for the most part it is surprisingly thin considering the evident abnormality. On section the entire liver is found to be divided into thousands of small round masses of sizes varying about as the nodules upon the surface. Nothing approaching the appearance of normal liver tissue is identifiable to the naked eye. The consistence of these masses is firm but by no means hard. The liver as a whole, is somewhat firmer than normal but has not that absolute leathery feeling common to advanced cirrhosis. The cut surface of the nodules seems somewhat paler than the nodules appear on the outer surface, whether they are bile stained or not. Each mass seems to be surrounded by a fine connective-tissue capsule.

The gall-bladder wall is much thickened, but the mucosa, though pale, is normal in appearance.

The portal veins are clear throughout. No thrombi or other obstructions and no dilatations are found in them or their tributaries.

Microscopic Description. The lungs are normal except for the presence of the infarcts and slight congestion and edema.

The heart muscle is normal.

The spleen shows a slight chronic interstitial splenitis. The two small accessory organs have a normal splenic structure.

The kidneys: The right shows slight hemorrhage. The left is normal.

The mesenteric lymph nodes, stomach, and intestines are normal.

The liver: The blocks of tissue studied were fixed in formalin. The paraffin, celloidin, and freezing methods were used. The sections were stained in hematoxylin-eosin, eosin-methylene blue, Mallory's connective-tissue stain, v. Gieson's stain, safranin, phosphotungstic acid hematoxylin, and scharlach R.

FIG. 1.—Adenoma of the liver, showing under surface. Note large size of the nodules and the great enlargement of the left lobe.

As the sections from the different portions of the liver are gradually gone over, the first point which impresses one is the almost total absence of normal or even relatively normal parenchyma. In its stead one sees a picture composed of generally round masses of cells of different sizes, each surrounded by a definite capsule. At first one is inclined to believe each mass derived from an original lobule of the liver, but on closer inspection, this structure is nowhere definitely preserved. Sometimes one sees what appears to be the remnant of a central vein but in most cases even this is absent. An occasional portal space has survived the change sufficiently to be recognizable. The arrangement of the cells corresponds in places to that of the normal parenchyma, but the likeness is limited, however, to the fact that the cells form minute bile-ducts, and seem to be disposed about a lumen which in some instances is apparently filled with a cast composed of closely

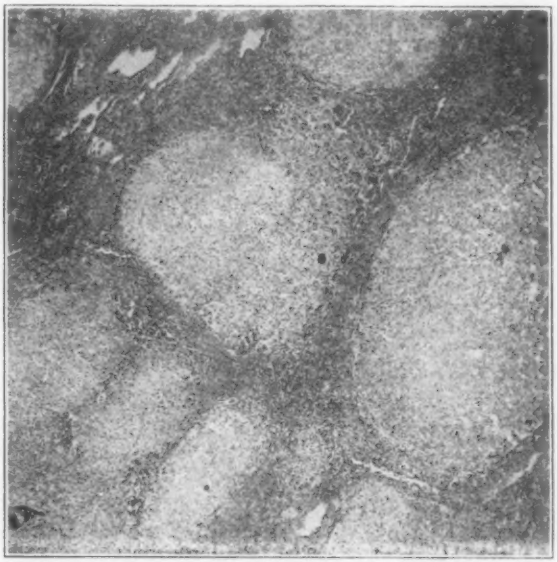

FIG. 2.—Adenoma of the liver (× 70). Single encapsulated nodules. At lower left corner are parts of four lobules coalescing to form a new adenoma nodule.

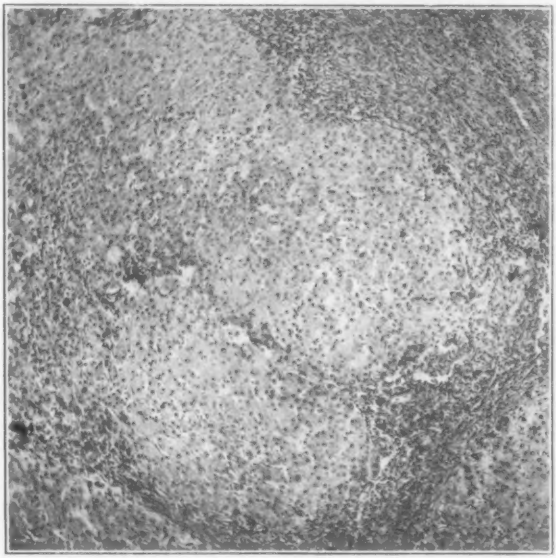

FIG. 3.—Adenoma of the liver (× 200). Same location as in Fig. 2. Cells brought out more clearly.

packed masses of pigment granules and detritus. In the majority of cases the cell masses are mere groups with no definite arrangement like that of the liver cells. They are noticeably poorly supplied with bloodvessels for the most part. Some, however, have quite a number of small twigs running along between the duct-like strands of cells (Fig. 4). In all instances they arise from the capsular vessels.

FIG. 4.—Adenoma of the liver (× 800), showing details of the cells and their likeness to the normal cells of the liver. Note the double nucleation of some of the cells and the pigment casts of the ducts.

The cells are polygonal in shape, but not as sharply polygonal as are the normal cells. These tend to be rather more rounded and irregular. No columnar cells are seen, neither are there any reversions to embryonic type. The characteristic cell is much larger than that of the liver cell, and may be three or four times its size. Usually their size is definite for a certain mass, one mass containing only large ones, while another is made up of much smaller cells. The size of the cells is generally much greater than usual in sections taken from the deeper portions of the organ and coincidentally the deposit of pigment in the cells and between them, which is widely distributed, is much more prominent in these deeper portions. The pigmentation is in the form of granules of coarse and finer sizes which often packs the cells to such an extent that their morphology is totally obscured. It is partly

hematogenous and partly biliary in origin, the hematogenous granules coming out clearly by the ferrocyanide-HCl test in frozen sections.

The cells when not obscured by pigment show a clear, homogeneous protoplasm, and with some stains, particularly v. Gieson's, the cell body takes on an almost glairy appearance. The protoplasm takes a light pink stain with eosin-methylene blue and a slightly darker hue with hematoxylin-eosin. In the sections stained by v. Gieson's stain there is marked variation of the protoplasmic stain, those cells in what seems the older portions taking the lightest coloring and some having totally lost their staining capacity. The cells rest on a delicate basement membrane, which stains clearest in the phosphotungstic acid hematoxylin preparations. No intercellular bridges of any kind are seen.

The nuclei are uniform in size, irrespective of the size of the cells. They take a pale blue stain in the eosin-methylene blue preparations and show no marked chromatin network. A good number of cells are doubly nucleated, and in these the daughter nuclei are darker than the others, and have a more decided chromatin network. Wherever it can be determined, these nuclei have always divided by simple fission. The very few examples of karyokinesis observed in the safranin-stained sections do not show any remarkable characteristics.

The masses of cells are surrounded by strands of connective tissue of moderate thickness and density. Near the junction of several of these cell groups the areas of connective tissue are of considerable extent, and, indeed, throughout the sections the amount of connective tissue and its arrangement at first suggest cirrhosis. With closer study some facts appear which seem in our judgment to controvert this idea. In the first place the lobule of the liver as such is not the histological unit giving rise to these growths. In the multilobular or Laennec's type of cirrhosis we see small groups of lobules surrounded by bands of connective tissue, the latter conforming more or less closely to the outlines of the lobules in the group; nevertheless we never see the connective tissue splitting up several lobules, including half the resulting divisions in a single group and entirely leaving out the other portions. In this case, however, there appears to be a somewhat analogous process going on. There are certain areas where the adenomatous transformation is not complete. In these instances there is apparently a centre of transformation in one portion of a lobule from which the adenomatous change gradually spreads, slowly involving parts of neighboring lobules. The capsule forming about this newly evolved growth creeps around the adenomatous portions and merges them into one mass, the other and normal portions remaining outside the capsular wall.

Again, of the two processes, cellular growth and connective-

tissue proliferation, the latter seems relatively much younger and is certainly much younger than a like amount of cirrhotic connective tissue. Only in the deeper and older portions of the growth is there any density and tendency to hyalinization, and in contradistinction to this the cells in these locations show disintegrating nuclei, poorly and unevenly stained protoplasm, which is often hyaline, and even large areas that have undergone degeneration and become necrotic. Nor do we see the bile-duct formation to anything like the extent seen in nearly all cases of cirrhosis approaching this grade of connective-tissue formation. In places one sees areas of relatively normal but greatly compressed liver cells. That these are groups composed of many lobules can be easily seen, and here it is noteworthy that the connective-tissue growth is entirely absent, the compression being the result of the pressure of the surrounding cell masses and their capsules.

Nowhere in the sections do we see any intercellular or intralobular connective-tissue invasion except to the slightest extent. Such invasion as can be seen is brought out only by the special connective-tissue stains.

There are several areas, as above mentioned, where it is possible to see a direct change in the parenchyma from the normal to the adenomatous type. It is significant that the connective-tissue capsules surrounding them are rudimentary in comparison to the capsules of the older growths. In these newer portions the connective-tissue cells are younger and more nearly of the fibroblastic type, and there is no hyaline change visible. The amount of the fibrous proliferation seems proportional to the completeness of the transformation to the adenoma structure.

In the larger areas of connective-tissue formation one sees many large and small bile-ducts which in most cases are dilated. They are lined by cuboidal epithelium, and in many instances are filled with great masses of granular pigment of biliary origin.

No tendency to malignant transformation is anywhere noted. No new growth of any kind is seen anywhere else in the body.

We have here, then, a case of adenoma of the liver whose multiple nodules have replaced the liver substance to such an extent that only microscopically can any normal liver tissue be found. They are derived from the liver parenchyma itself, instances being seen of transformation in progress. Each tumor nodule is encapsulated. That this connective tissue is not the manifestation of a cirrhosis is demonstrated by: (1) Individual nodules do not spring from original individual lobules; (2) parts of many lobules are united in some instances to form the tumor nodules; (3) where the neoplasmic transformation is in progress we find these parts surrounded by only rudimentary capsules; (4) the few areas of normal though compressed liver tissue visible are not invaded by a connective-tissue overgrowth such as one would expect if the condition were

one of cirrhosis; (5) there is no fatty metamorphosis, malignant transformation, other tumor formation or any abnormality of the portal veins.

The case herewith reported is of interest because (1) it presented the symptom complex of Hanot's hypertrophic biliary cirrhosis; (2) because the study of the liver does not bear out the generally accepted view that multiple adenomata are always secondary to and in compensation for liver cirrhosis; (3) because it shows the importance of recognizing the fact that symptoms identical with those produced by either the atrophic or the hypertrophic form of cirrhosis may take their origin from multiple adenomata.

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REVIEWS

DIGESTION AND METABOLISM. THE PHYSIOLOGICAL AND PATHOLOGICAL CHEMISTRY OF NUTRITION. FOR STUDENTS AND PHYSICIANS. By ALONZO ENGLEBERT TAYLOR, M.D., Rush Professor of Physiological Chemistry, University of Pennsylvania, Philadelphia. Pp. 560. Philadelphia and New York: Lea & Febiger, 1912.

BEARING the signature of one of America's greatest exponents of the philosophy of science, this book by Taylor deserves a careful perusal by its readers. Let not the student or physician for whom this book is written, sigh hopelessly as he buffets with lusty sinews the raging scientific tenent of the first two chapters, for it is in these two chapters that the most difficult channels are found. Even the modern student (for we understand Professor Taylor to mean the undergraduate) with the advantage of the newer scientific training, will find the reading of these two chapters a most arduous undertaking, but the physician, and we understand his prototype to be the practitioner, will we fear, not trust himself to embark on such a flood. These two chapters to the reviewer's mind, are the most difficult of comprehension. Dr. Taylor, whose work with ferments needs no mention, treats his favorite theme in a manner as clear as is the question of fermentation itself, and therefore he bewilders us. His grasp of the subject is no doubt firm, but his exposition thereof is obscure at times, due we believe to his thorough knowledge which presupposes students and physicians to be in lesser degree, as fundamentally well informed as is he himself. In justice to the author, we must express our conviction that the abstruseness which we find, is due mostly to the recondite nature of the subject. Furthermore, we must acknowledge that few authors could so adequately depict the *modus operandi* of catalytic acceleration or fermentation.

The chapters on "Digestion" and "Metabolism" (*in toto*) are those on the metabolism of certain food stuffs, are excellently penned, and are pregnant with information bearing the hall mark of the writer's great experience. For instance, sound argument against the use of indoxyl, conjugate sulphates, and other waste products, as an index of intestinal putrefaction, is offered in such a form that refutation of Taylor's views seem impossible. We

have read much on this subject, but nowhere is it handled so clearly in a few words as by Taylor. We admire also the chapter on autointoxication, a name which has been so grossly misused as "to have lost concrete meaning," but regret, although the subject does not lie within the scope of this treatise, that the chapter should have been so curtailed.

To discuss in detail the many admirable features of this work, would mean more space than is allotted to this review, for the book is replete with valuable information, now easy of acquisition, a fact which must be regarded by all as a notable educational accomplishment. One must not estimate this volume as a text-book this it is not, and cannot be; but to the student (and the reviewer now applies this term in its broadest sense) who desires authoritative information on problems of digestion and metabolism it is especially recommended.

The work is distinctly original in conception and execution, and in this it differs uniquely from many of the too numerous scientific books. It represents an individuality and not alone a compilation, thereby giving the impression of something new and not merely an inheritance, thus acquiring an authoritative atmosphere which one somehow misses in most works. We felicitate the author on this notable result of his labors, and prophesy for it a distinct place in American scientific literature. E. H. G.

INTERNAL MEDICINE. By DAVID BOVAIRD, JR., A.B., M.D., Assistant Professor of Medicine in the College of Physicians and Surgeons of Columbia University; Associate Visiting Physician of the Presybterian Hospital, and Visiting Physician of the Seaside Hospital, in the City of New York. 109 illustrations and 7 colored plates. Philadelphia and London: J. B. Lippincott Company.

BOVAIRD'S book attempts to compress into less than 600 pages the whole of the subject of the practice of medicine. It holds, therefore, in size, a relation midway between the undesirable and now happily less popular compends and the large single volume medical works of which there is such a surfeit on the market. Despite the condensation all the essentials are to be found in the book, so that the student in particular will find it useful in preparing for his final examinations. But he must not think, as he is inclined to do, that he has covered the subject of medicine when he has read Bovaird's book or one of similar size. Such books, as well as the smaller compends, often create a false feeling of thoroughness. The student, it seems to the reviewer, should be urged to read important subjects, whether in internal medicine or in

surgery, in monographs, at any rate in one of the large medical works, so as to acquire a broader viewpoint and a little knowledge of the history of the particular subject he is studying. The reading of a compend or a book like Bovaird's cannot supply these desiderata.

The author's diction is good except that he has no mercy on infinitives and splits them ruthlessly. The appendix on the care of the sick and on diet add much to the usefulness of the book.

D. R.

PRINCIPLES OF HUMAN PHYSIOLOGY. By ERNEST H. STARLING. M.D. (Lond.), F.R.C.P., F.R.S., Hon. M.D. (Breslau), Jordell Professor of Physiology in University College, London. Pp. 1423; 564 illustrations. Philadelphia and New York: Lea & Febiger, 1912.

IN these times of overpublication the teacher of physiology is prone to look upon each new text-book on this subject as another useless product of the efforts of a physiologist unconsciously stimulated to the work by the keen business methods of one of the many publishers. Of the scores of text-books in this field less than a half-dozen have a justification for their existence. To write a satisfactory work of this kind requires an extremely broad as well as detailed knowledge of the subject in all of its branches, and at the same time a long teaching experience. Few men have these qualifications in this age of investigation which concentrates the attention upon one part of the subject. Investigators, when writing text-books, usually give entirely too much space to the subjects in which they are particularly interested. The finished product is consequently unbalanced. However, even a hasty survey of the latest book of Starling convinces one that the author has all of the qualifications of a successful writer of text-books. Upon closer perusal this opinion is justified in every respect. A reviewer is prone to read critically first of all those chapters which contain subject matter with which he is most familiar, but here the book stands the severest test. Again, when he turns to the chapters which contain the discoveries of the author he finds no material which is not of value to the student even though not specializing in physiology. The author shows an immense grasp of the subject, and combines with it a capability of clear description which makes every part of the book interesting.

The book is quite large, consisting of over 1400 pages, but one feels that it is not too large. Every page contains material which the earnest student will be interested to know. Nor would the practitioner, referring to the book upon any subject whatever, be satisfied with less than the author gives him. One cannot under-

stand why Starling could have felt the necessity of a manual such as he wrote a few years ago. It was an excellent work, but too brief for these times in which physiology has come to occuyy such an important and extensive position in biology and medicine.

In his last work, methods receive much more attention than is accorded them in other books of equal size, but this seems justifiable as the practical work in physiology which is given to the student in every good school, has created a desire among students not only to know that a thing is so, but also how it has been demonstrated. One shortcoming is the absence of references in the text which often is so convenient to the student who wishes to learn more of a subject.

After a brief introduction the author takes up the chemistry of the constituents of the organism in a brief yet thorough enough manner. This is followed by a chapter on the energetic basis of the body which contains much of the important material contributed to physiology by physical chemistry. The chapter is thoroughly up to date. The following subjects are considered: The energy of molecules in solution, passage of water and dissolved substances across membranes, the properties of colloids, the mechanism of chemical changes in living matter, and the electrical changes in living tissues. With this the author plunges at once into special physiology, considering first the mechanism of movement and sensation. Then nutrition in all of its phases is taken up, and finally reproduction. The chapter on the ductless glands is excellent. The physiology of pregnancy and reproduction is given more space than is usually allotted to this subject. Each chapter so far as the reviewer can judge, is well balanced, contains well selected material and clear descriptions. E. L.

DEFORMITIES, INCLUDING DISEASES OF THE BONES AND JOINTS. A TEXT-BOOK OF ORTHOPEDIC SURGERY. By A. H. TUBBY, M.S. (Lond.), F.R.C.S. (Eng.). Second edition. Vol. I; pp. 883; 603 illustrations. Vol. II; pp. 867; 483 illustrations. London: Macmillan & Co., Ltd., 1912.

THERE has been an increasing ambition in many of the physicians who have devoted their attention to orthopedic surgery, to produce a book on the subject to serve at least four purposes: (1) As a text-book for students; (2) as a reference book; (3) to bring together in a logical sequence the maladies which belong to the specialty, and (4) to emphasize the writer's views on conditions which absorb his especial interest. General and comprehensive collections of orthopedic facts have not been, nor could they be, entirely satisfactory. The scope of orthopedic surgery

can be fairly clearly defined if it be approached in the proper spirit. Orthopedic surgery should embrace defects common to the body mechanisms upon which position, motion, and locomotion depend. Freely abridging the subject, and the inclusion of conditions which do not belong to the specialty, should be reckoned with as faults. Tubby's work approaches to a gratifying degree the needs that have been keenly felt by the more advanced students in orthopedic surgery. It is too comprehensive for the academic student, it would confuse and encumber his first skeletal notions of the subject. Some of the cuts are crude and do not emphasize the topic discussed. Many of them are especially noteworthy. The two volumes of the work contain over 1000 cuts, 400 of which are original. Due credit is given to the authors of borrowed cuts, as well as to authors of ideas as to treatment and technique.

The logical and etiological arrangement of the subject matter has received very careful attention. The context is to the point, although there are a few instances where verboseness can be charged, yet clearness and finish do not suffer seriously. A vein of optimism is felt which adds encouragement but which carries a danger of imparting prejudice.

In this work there is not an offensive evidence of the author at every turn, nor is there an undue prominence of his views. It brings together the research, experiments, and experience of the leading orthopedic surgeons of the world in a very gratifying fashion; it is rich in bibliography. There is generally a pleasing diversification of opinion and methods of practice. Pathology and pathological anatomy have received a creditable amount of attention.

Conclusions are augmented by facts from the author's and other men's hands, varying results are given frequently, which favor unbiased opinions.

The thought that there is a lack of predominating originality arises in one's mind as he inspects the work, its creation, however, entailed an enormous amount of labor for the author and his collaborators. Too much credit cannot be given for the indefatiguable energy with which the author pursued his task in compiling this diversified and orderly work. W. J. M.

SEXUAL IMPOTENCE. By VICTOR C. VECKI, M.D., Mt. Zion Hospital, San Francisco. Fourth edition. Pp. 394. Philadelphia: W. B. Saunders Company, 1912.

THE fourth edition of this book is revised and enlarged. It is written in a clear and bold style, and is stamped with the author's

individuality. The chapters on anatomy, and especially physiology, are more complete than one usually finds in a work of this kind. In considering the etiology of impotence the author recognizes the difficulties of classifications upon scientific basis, and divides the various causes into seven groups for convenience of description. One-half of the work is devoted to the various causes under no less than eighty-two headings. Masturbation, resulting in morbid pollutions and spermatorrhea, is regarded as the essential cause of impotence. The injurious effects of sexual excesses on the functional capacity of the sexual organs are considered more exaggerated than underestimated, and excessive continence may result in constitutional and sexual injury. Gonorrhea, its complications and sequelæ, conceded by many urologists to be of considerable importance in the etiology of impotence and allied sexual derangements, receives scant attention. In considering the treatment many drugs are discussed, and due attention paid to hydrotherapy, electrotherapy, organotherapy, mechanical devises, and general constitutional treatment. Local treatment is recommended when indicated, and a wise protest is entered against too severe urethral treatment. The book, as a whole, represents the author's personal views, and from this standpoint is to be commended. There is little doubt, however, that he attributes to onanism an etiological importance which is unwarranted, and spermatorrhea so frequent in his experience is seldom encountered in the experience of others. There is also no foundation for the belief that sexual continence is followed by a decadence in bodily health or virility. A. A. U.

FATIGUE AND EFFICIENCY. A STUDY IN INDUSTRY. By JOSEPHINE GOLDMARK, Publication Secretary, National Consumer's League. Pp. 893. New York: Charities Publication Committee, 1912.

"FATIGUE and efficiency" are representative of the new effort to inquire into the conditions of modern industry and to interpret them for the people at large in the light of physiological laws. The effects of overwork is the subject of a discussion at once practical and illuminating. In her effort to treat the question of fatigue from every possible point of view, Miss Goldmark has drawn her information from a dozen sources: the laboratory, the shop, the home life of the workers themselves.

The book has two divisions: (1) A discussion of the whole subject of fatigue in its dual relation, its effect on the product and its effect on the workers. In this connection, the title of ths book perhaps implies that the author lays the greater emphasie on the economic result. As a matter of fact, she does prove con-

clusively that a system compelling long hours of labor must result in a deteriorated output; yet it is evident that her primary concern is in the fact that its most far reaching and disastrous results are deteriorated human beings.

Of special interest to the physician are the chapters presenting a study of the relation of fatigue to infant mortality and race degeneration. The author's conclusions are summed up in the sentence: "When overwork unfits man or woman for normal parenthood, it is in a deep sense antiphysiological and antisocial."

In the light of the general principles relating to the results of fatigue the author presents a detailed study of a number of industries which employ women, such as the canneries, the shoe manufactories, and the telephone service. She describes the effects of fatigue that are caused not only by too long hours, but by what she calls the "new strain in industry," induced by noise, monotony, the rigid rhythm of machinery, and abnormal speed and complexity. Aside from diseases connected with specific kinds of work, the author says that the most deplorable of all the physical evils of fatigue is that it prediposes its victims to disease in general. For this reason she urges that there be a "new medical scrutiny of modern work" centred on "fatigue as itself a danger of occupation."

(2) The second division of the book given the material contained in four briefs in defense of laws especially related to women-employing industries which were filed in various courts by Louis D. Brandeis. These briefs are gathered under the significant heading, "The World's Experience upon which Legislation Limiting the Hours of Labor for Women is Based." As the title implies, they are really a symposium of conclusions in relation to fatigue which the author has gathered from the experience of various scientists, social workers, and employers of all countries.

The work is of primary value as a practical handbook for all interested in the amelioration of industrial conditions. It is written for the average reader. With its careful tabulation of facts and simplicity of thought and expression it is intelligible alike to the physician and lawyer, to the employer and social worker: in fact, even to the workers themselves whose cause it so ably champions.

H. G.

THE MEDICAL RECORD VISITING LIST FOR 1913. New York: William Wood & Co.

THIS convenient little record book contains pages for daily and special visits; memorandum pages and pages for cash accounts. In addition there is a certain amount of information that may be of service for quick reference which includes dosage, treatment of poisoning, artificial respiration, and such subjects.

J. H. M., JR.

AN OPERATING THEATRE IN PRIVATE PRACTICE. By C. HAMILTON WHITEFORD, M.R.C.S., L.R.C.P. Pp. 76. London: Harrison & Sons, 1912.

THE author describes the building and equipment of an economical operating plant employed by him in connection with his private practice. It is well adapted to the needs of a surgeon living in a small town without the facilities of a large general hospital. Many of the original ideas in the book could be well copied in the operating rooms of large hospitals. The lighting of the room is by a large window facing south which the author finds well suited to the English climate, being neither too hot in summer, and affording better light in winter. The fixtures are arranged as much as possible flush with the walls, thus avoiding lodgement for dust. Among interesting features noticed are, an electric heating appliance for the operating table, a simple and efficient arm retainer, and a convenient receptacle for nail brushes. Valuable points on technique from the author's personal experience are given, as to sterilization, sutures, anesthesia, preparation, and after-treatment of the patient, etc. In an appendix are found useful facts on asepsis for nurses. The work would have been more complete if illustrated by a diagram. It can be recommended to anyone contemplating building an operating room either for private or general work. R. H. I.

A MANUAL OF CLINICAL CHEMISTRY, MICROSCOPY, AND BACTERIOLOGY. By M. KLOPSTOCK and A. KOWARSKY. Pp. 371; 43 illustrations; 16 plates. New York: Rebman Company, 1912.

THIS book is a translation of a valuable laboratory manual which covers not only the technique of the common clinical laboratory examinations, but also that of some less familiar that are of use in the study of the secretions of the conjunctiva, nose, mouth and pharynx, and of the sputum, gastric contents, urine, feces, blood, puncture fluids, and skin. Throughout the book much attention is devoted to bacteriological procedures, which are, for the most part, described in detail. The value of the volume is, however, seriously impaired by the extraordinary character of the translation of some portions. In a footnote on the first page the statement occurs: "All degrees of temperature quoted in this book are Celsius." For American readers "Centigrade" should have been used instead of "Celsius." In the first chapter the German "Klatsch-preparata" is never translated to the equivalent "cover-slip preparation." One is tempted, however, to close the book on coming to such a sentence as the following: "Diphtheria bacilli decompose dextrose and levulose under acid formation,

pseudo-diphtheria bacilli, as proven in numerous types of various origin are almost always inactive in both kinds of sugar, and, but in rare cases, they are active in one, never in both." Or this: "Regarding their motility the views are divided. Some authors believe them to be immovable." Or this: "They (spirochete) are corkscrew-shaped, very motile in shape and size, however, very much different from each other." Even more serious is the error on page 7, where the statement is made that "Ox serum is rendered sterile by *discontinuing* sterilization at 55°." The correct reading is "by discontinuous sterilization." Fortunately no other chapter contains errors as absurd as those which render the first chapter more ludicrous than useful. The section on the Wassermann reaction is not entirely clear, being especially indefinite in that portion dealing with the titration of amboceptor and complement. On the other hand, the sections on gastric contents, feces, and urine are of great value, and include material not found in other laboratory manuals. The section devoted to the blood is brief and less complete. It is unfortunate that the value of so excellent a manual is diminished by imperfections in translation.

J. H. A.

ARTHRITIS: A STUDY OF THE INFLAMMATORY DISEASES OF JOINTS. By PETER DANIEL, F.R.C.S., Senior Surgeon, Metropolitan Hospital; Surgeon to the Gordon Hospital; etc. Edited by JAMES CANTLIE, M.A., M.B., C.M., Aberd., F.R.C.S. Eng., Surgeon, Seamen's Hospital Society; Lecturer on Surgery, London School of Tropical Medicine. Pp. 515; 131 illustrations. New York: William Wood & Co.

WITH an apology for unorthodox views, Cantlie has edited for Daniel a volume purporting to be a "study," but in reality more nearly resembling a student's compend.

It is crowded with matter, old and new, for the most part somewhat dogmatically expressed. Daniel, however, has evidently seen and considered an amount of clinical material which justifies some individuality of opinion, and enables him at times to advance points of value.

The text is punctuated by capitals, italics, and parallel tables to a rather unfortunate degree, even though the book is designed as a "practical help." In respect to scope and breadth of purpose, it deserves a wider field.

The illustrations, which are numerous, are usually semi-diagrammatic, but sometimes so inartistically done as to offend the reader in this age of pictorial excellence.

The English is careless, frequently loose enough to obscure the meaning, and at times ungrammatical. The book is rather heavy, and the type good. It is to be regretted that this possibly useful effort must be so heavily discounted. R. P.

A Text-book of Human Physiology, Including a Section on Physiologic Apparatus. By Albert P. Brubaker, A.M., M.D. Fourth edition. Pp. 736; 377 illustrations and 1 colored plate. Philadelphia: P. Blakiston's Son & Co., 1912.

It is pleasing to note that this excellent text-book has met with such a well-deserved demand as to require a fourth edition. Those who have had a long experience with students can see evidence upon every page of the fact that Professor Brubaker is an excellent teacher. When presenting a problem he has mastered the art of knowing where to start. Too often authors of the text-books now generally used, assume that the student's general knowledge of anatomy, histology, physics, chemistry, and even biology is such that they are free to plunge at once into a discussion of physiological material of the most intricate sort. It is true that the preparation of the student in the fundamental subjects leading to physiology is constantly improving, nevertheless, much of the data requires a thorough knowledge of details which are not given an important position or are entirely neglected in the presentation of the fundamental subjects. In consequence, a problem sometimes cannot be understood even by a well-prepared student, because he is not sufficiently familiar with the particular data from which the investigations start. This book does not neglect such data and therefore contains more histology, etc., proportionately than is found elsewhere, but, although starting a problem from the beginning, the book is never tedious for the necessary material is very briefly stated. This is shown by the size of the book which hardly exceeds 700 pages yet contains all of the physiology required in any of the best medical schools.

This edition also shows the intimate knowledge which the author possesses of the requirements of the up-to-date student and practitioner. He gives sufficient consideration to all of the physiological problems and methods which are interesting the medical profession today. For example, he goes into the subject of venous pulse in a most satisfactory manner. Likewise the pituitary bodies and the adrenal glands are considered from a physiological standpoint in a most conservative yet thorough manner. Even the finer points such as the auscultatory method of determining blood pressure is referred to. These are, however,

only a few of the instances which convince one that the book is in every way equal to the requirements of the student and practitioner.

It is pleasing to see too that the author does not avoid what are usually considered uninteresting subjects, provided they are of practical value. The physiology of the skeleton, so important to the practitioner, is often given brief consideration or entirely omitted in many books of this size. Recognizing the inestimable value of the subject in medicine the author has devoted an entire chapter to the skeleton and it has proved one of the most valuable in the book. E. L.

PATHOLOGY OF THE EYE. By P. H. ADAMS, M.A., M.B., D.O. Oxon., F.R.C.S., Surgeon to Oxford Eye Hospital; Consulting Ophthalmic Surgeon to the Radcliffe Infirmary. London: Oxford University Press, 1912.

THIS is an excellent little manual. It takes up in turn the different structures entering into the formation of the organ, gives a brief anatomy and then describes the appearances caused by the various disease processes as they occur in the special tissues. The introductory chapter gives a short account of the methods of embedding, mounting, staining, while the last chapter is a brief description of the bacteriology of the eye. The descriptions must necessarily be brief in a small work like the present and this is about the only criticism to be made, they are almost too brief—a criticism not directed against the author, who has succeeded very well indeed with the limited space at his disposal, but one which is inherent in the plan of the work. The book is hardly adapted to the novice who requires more detailed description but rather we presume as a sort of *vade mecum* for the reader who has some acquaintance with the subject. It need scarcely be said that the recent discussions, not to say, final results find a place; thus the Chlamydozoa in trachoma together with the method of staining are described; there is a short account of retinal arteriosclerosis, etc. We note that of the varieties of choroidal inflammation syphilis and tubercle are alone mentioned.

The book is attractively gotten up; it is convenient in size; the paper, type, and binding are all that can be desired. T. B. S.

PROGRESS

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MEDICAL SCIENCE

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UNDER THE CHARGE OF

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The Relation of Aortitis to Syphilis.—CUMMER and DEXTER (*Jour. Amer. Med. Assoc.*, 1912, lix, 419) demonstrated a positive Wassermann reaction in the sera of 27 cases of aortic disease in a series of 36. This is 75 per cent., and is almost identical with the larger series by Longcope (74.1 per cent. of 182 cases). Seventy and three-tenths per cent. of these were men, and Cummer and Dexter think that this suggests the possibility of the conjunction of hard labor with syphilis determining the aortic location. Most of the cases were men who had been occupied as day laborers, masons, brick-layers, etc. The average number of years since the appearance of the chancre was about seventeen. The process is distinctly a late one, and the period of latency a long one. Cummer and Dexter emphasize the indefiniteness of symptoms—pain referred to the upper sternum, a sense of constriction, dyspnea, and dulness in the second intercostal spaces extending to the left and right of the manubrium. Alleviation of pain occurred after mercurial treatment, which is urged so long as the Wassermann reaction is positive, with the hope of arresting the process.

Prophylactic Vaccination against Epidemic Meningitis.—Encouraged by the wonderful results obtained by extensive prophylactic typhoid vaccination, SOPHIAN and BLACK (*Jour. Amer. Med. Assoc.*, 1912, lix, 527) undertook to employ similar methods of prophylaxis against epidemic meningitis in the recent Texas epidemic. They emphasize the need of prophylactic measures when it is estimated that the number of healthy carriers exceeds the sick by ten or twenty times. The vaccine consisted of a killed culture five generations old, sterilized by

heat, and standardized. Eleven students were vaccinated at seven-day intervals, with three doses of 1,000,000,000 2,000,000,000, and 2,000,000,000 bacteria respectively. A slight leukocytosis followed, with malaise, headache, and fever. Occasionally signs were present suggesting meningeal irritation—severe headache, vomiting, vertigo, and photophobia. A local reaction with redness and swelling, and adenitis is the rule. The reaction lasts twenty-four hours. The immunity acquired was measured by agglutination and complement-fixation tests. The agglutinins increased after the repeated doses, one patient developing them to a liter of 1 to 1500 dilution of the serum. The highest complement-fixation was obtained in serum dilution of 1 to 250, at the end of the third week. All evidence points to the efficacy of the injection of dead meningococcus for prophylactic vaccination, as a measure which will confer considerable immunity in most cases against the infection of epidemic meningitis. The cases will be followed to determine the persistence and duration of the immunity.

Endemic Typhus Fever (Brill's Disease).—NICOLL, KRUMWIEDE, PRATT, and BULLOWA (*Jour. Amer. Med. Assoc.*, 1912, lix, 521) report a unique instance in the history of the endemic form of typhus fever (Brill's disease), in which the disease affected four members of the same family, two parents and their children. Clinically they represent types of the disease varying from the comparatively mild to an example of typhus fever such as is commonly seen in epidemics, thus giving, as it were, a clinical demonstration of the identity of the endemic and epidemic forms. The patients were Russian Hebrews of the poorer class and all were infested with head and body lice. Inoculation of the blood of one of the patients gave positive results in two guinea-pigs whose blood, in turn, injected into a monkey, caused a typical typhus temperature reaction. The authors have shown for the first time that it is possible to infect guinea-pigs with the disease, an additional point of similarity to the epidemic type.

Treponema Mucosum and Pyorrhea Alveolaris.—NOGUCHI (*Jour. Exper. Med.*, 1912, xvi, 194) isolated a small spirocheta from the pus of a case of pyorrhea alveolaris which is characterizeed chiefly by its capacity to produce mucin and a strong fetid odor. It is an anaërobe, and requires the presence of serum constituents for its growth. Subcutaneously it produces an acute inflammation and the tissues remain indurated a week or ten days. But there is no tendency to suppuration. The organism is easily differentiated. It has been named Treponema Mucosum and Noguchi holds it at least in part responsible for the strong fetid odor in the discharge from pyorrhea alveolaris.

Experimental Bronchopneumonias.—Following the experimental production of lobar pneumonia by intrabronchial insufflation of pure cultures of pneumococcus (Lamar and Meltzer), the advisability was suggested of applying the same method to the action of organisms usually found in association with bronchopneumonia. This was done by WOLLSTEIN and MELTZER (*Jour. Exper. Med.*, 1912, xvi, 126). Cultures of the streptococcus and influenza bacillus were injected

through a tube deeply into a bronchus. With the streptococcus 19 dogs killed at intervals showed typical pneumonic lesions in various stages of progression and resolution. Compared to the mortality of 16 per cent., the bacteriemia, the lobar consolidation, the frequency of pleurisy, and the importance of fibrin formation in the experimental pneumococcus pneumonias of Lamar and Meltzer, these streptococcus infections showed practically no mortality, no bacteriemia, a lobular type of consolidation, no pleurisy, and an unimportant part played by fibrin. The same held true for the influenza bacillus. Wollstein and Meltzer conclude that the proper invasion of the microorganism is the determining factor in the development of pneumonia, the condition of the animal being only a minor element. Different types of pneumonia are produced by specifically different bacteria.

The Cobra Venom Hemolysis Test in Syphilis.—For about five weeks after the primary lesion in syphilis the red cells are hypersusceptible to cobra venom hemolysis in all dilutions. After this they acquire tolerance and become resistant to this hemolytic agent. In no other condition or disease does this occur. STONE and SCHOTTSTAEDT (*Arch. Int. Med.*, 1912, x, 8) have applied this test to 130 patients. The wasted corpuscles are mixed with cobra venom in dilutions of 1 to 10,000, 1 to 15,000, 1 to 20,000, and 1 to 30,000. All bloods hemolyze in 1 to 10,000; all normal bloods in all dilutions; in secondary syphilis the cells resist in dilutions above 1 to 10,000. In 4 cases of primary syphilis the test was positive (resisting hemolysis) in only 1. In 22 cases of active secondary and tertiary syphilis, 20 or 90.9 per cent. were positive. Thirty-three cases of latent secondary and tertiary syphilis yielded 87.8 per cent. positive. In 20 "clinically cured" cases the reaction was uniformly negative. Compared to the Wassermann reactions, an average positive percentage of 88.5 per cent. in 4200 cases of active syphilis, the cobra venom test gives about the same results, 85.4 per cent. positive in 1279 cases. But for latent syphilis, the positives averaged 78.1 per cent., compared to only 52.1 per cent. of Wassermann positives. The cobra venom and butyric acid tests agreed in 85.4 per cent. of 13 cases. Controls were negative.

The Wassermann Reaction Post Mortem.—H. SCHMIDT (*Deutsch. med. Woch.*, 1912, xxxviii, 802) has examined the sera of 233 cadavers for the Wassermann reaction. In many instances determinations had also been made during the life of the patient, in some cases as long as six months before death. Incomplete hemolysis was designated as a positive reaction. Of 34 luetics whose sera were examined both before and after death, corresponding results were found in 31. In older cadavers Schmidt finds that the serum may be examined in the active state. In this case a negative reaction is of considerable value, but if the reaction is positive, a control with inactivated serum must be made. In 94 per cent. of cases, lues in any form may be determined by examination of the serum obtained at autopsy. However, it must be remembered that in tumor cachexias, severe tuberculosis, and sepsis, the reaction may at times be positive, though the hemolysis is usually incomplete. Schmidt believes that the reaction possesses a relatively high value at autopsy.

Decreased Resistance of the Erythrocytes after Consumption of Alcoholic Drinks.—F. v. FILLINGER (*Deutsch. med. Woch.*, 1912, xxxviii, 999) has repeated and confirmed v. Liebermann's observations upon the lowering of the resistance of the erythrocytes after drinking alcohol. His observations were made on man and animals. The technique he employed is the same as that described by v. Liebermann. Only a few observations are reported, but they appear to show that alcoholic drinks produce a marked, rapidly developing decrease of the erythrocytes to hypotonic salt solution in persons whose bodily resistance is already somewhat below par. The phenomenon is of short duration. Measurement of the resistance of the red cells to 0.5 per cent. salt solution is thus not only a means of determining the resistance of the individual, Fillinger contends, but it is also a convenient method of determining directly injury to the organsim by alcohol and of following the extent of the injurious effect. It is desirable that similar observations be made on chronic alcoholics.

The Diagnosis of Internal Injuries Affecting the Pancreas.—J. WOHLGEMUTH and Y. NOGUCHI (*Berlin. klin. Woch.*, 1912, xlix, 1069) call attention to the difficulty of diagnosticating injuries to the pancreas as a result of severe trauma of the abdominal wall. At present, there are only two methods of procedure—exploratory laparotomy and observation of the patient for a variable time. It is, therefore, desirable to have some means of ascertaining pancreatic injuries within a few hours after the traumatism has occurred. Wohlgemuth has shown that lacerations of the dog's pancreas give rise to a rapid and marked increase in the quantity of diastase in both blood and urine. The method he employed required twenty-four hours for its completion, which is a great disadvantage in the study of human cases, and he has, therefore, so modified it that the result may be obtained in one-half hour. The method is as follows: 4 to 5 c.c. of blood are defibrinated and centrifugalized at once to obtain the serum. A series of ten test tubes, numbered, is then prepared and filled with serum. Tube No. 1 contains 1 c.c. of serum, No. 2 contains 0.5 c.c., and so on, to tube No. 10, which contains 0.002 c.c. of serum. The quantity of serum added is thus one-half the quantity placed in the preceding tube of the series. To each of the test tubes now add 2 c.c. of 0.1 per cent. starch solution (Kahlbaum's soluble starch) and place all the tubes in a water bath at 38° to 40° C. for thirty minutes. Remove the tubes, cool them quickly, and then add fiftieth normal iodine solution a drop at a time. The tube in which the first bluish tint appears, is noted. It is then evident that the next preceding tube in the series, which showed no blue color, contained sufficient diastase to convert all of the starch into dextrin. Knowing the quantity of serum in this tube, which has converted 2 c.c. of starch solution to dextrin, the amount of starch solution, which 1 c.c. of serum would convert, is calculated. The result is expressed thus, $d^{38°}_{30'} = 32$, for example. Using this method with normal human sera (150 cases) Wohlgemuth and Noguchi found the normal value to be 8 to 16; the highest normal value found was 32. Thus, if a lesion of the pancreas is suspected in a patient who has received a severe blow on the abdomen, a value of 64 greatly strengthens the supposition. The diagnosis

is practically certain if the quantity of diastase rises. The examinations must be begun soon after the injury. Beyond seventy-two, or, at the most, ninety-six hours, the diastase will probably have returned to normal. The increase is attributed to escape of pancreatic juice into the peritoneal cavity, with subsequent absorption into the blood. Since the increase of blood diastase leads to increase of the urinary diastase, the urine should also be examined for confirmatory evidence. Normally, in the urine of man $d_{\frac{3}{5}0'}^{\frac{8}{5}0^\circ}$ = 16 to 32; it never exceeds 64. In 2 human cases Noguchi has used this method with success. The work will be reported by him in detail in the *Archiv f. klin. Chirurgie.*

Fatty Stools in Basedow's Disease.—A. Bittorf (*Deutsch. med. Woch.*, 1912, xxxviii, 1034) reports a case of severe exophthalmic goitre, in which fatty stools were observed. Falta reported 6 similar cases in 1910 and assumed that the condition was due to a disturbance of the internal secretion of the pancreas, though in his cases the external secretion was apparently not examined. In the present case, Bittorf has shown that there was an insufficiency of the external secretion. There was almost a total absence of trypsin and an excess of unaltered muscle fibers in the feces. After the administration of pancreon, the fat content of the dried feces sank from 50 per cent. to about 17 per cent., the fat loss in percentage of fat intake from 60 to 75 per cent. to 14 to 15 per cent. Alimentary glycosuria could not be tested in this case, but Bittorf has frequently observed it in Basedow's disease, and believes that there is no relation between fat and carbohydrate derangements in this disease.

The Treatment of Rat-bite Disease with Salvarsan.—S. Hata (*Münch. med. Woch.*, 1912, lix, 354) has collected the data of 8 cases of rat-bite disease, occurring in various parts of Japan, all of which were treated with salvarsan. The salvarsan was administered at different stages of the disease and also in the febrile and afebrile periods. In all instances the injection of salvarsan produces a striking result. Except in 3 cases, a single intravenous injection sufficed to prevent further manifestations of the disease. There was observed, however, a rise of temperature in the night following the injection or several days later, but none of the other characteristic symptoms of the paroxysm was present. Hata interprets this elevation of temperature as a reaction from the drug. With defervescence there was a marked and rapid improvement of the general condition of the patient, the inflammatory processes disappeared, and the exanthem cleared up. Gradually the tumefaction of the lymphatic glands went down, and within a few weeks the patients were well. In 1 case, however, a cure was not obtained, though there was great improvement. In 2 cases recurrences were met with, but the dose of the drug employed was too small. Hata is unwilling to say that salvarsan is a specific in rat-bite disease, but the results are better than those obtained with other forms of treatment.

The Differentiation of Human and Bovine Tubercle Bacilli by Cutaneous Infection of Guinea-pigs.—E. Tomarkin and S. Peschic (*Deutsch. med. Woch.*, 1912, xxxviii, 1032), at the suggestion of Prof.

Kolle, have undertaken to determine whether human and bovine strains of tubercle bacilli may be differentiated by their varying virulence to guinea-pigs. The procedure they have employed consists in shaving the skin of the abdomen and then rubbing a measured quantity of the infectious material into the skin for two to three minutes, using a glass rod. With ordinary care the skin may be shaved so that there are no abrasions visible on inspection with a hand lens. The material they used for inoculation was obtained from various sources, that is, human tuberculous cultures, sputa, urine, and cavity contents, and bovine tuberculous cultures and glands. Tomarkin and Peschic found that the great majority of animals inoculated with human material remained healthy (of 52 guinea-pigs only 7 developed tuberculosis), whereas all animals inoculated with bovine material—whether cultures or diseased tissues—developed tuberculosis of the regional lymphatic glands and, later, generalized tuberculosis (26 guinea-pigs in all). They noted further that in none of the animals did local signs develop at the site of inoculation. Whenever infection occurred, the regional lymphatic glands were first enlarged. This striking difference in infectivity Tomarkin and Peschic attribute to variation in virulence of the two types for the guinea-pig. The study is being continued.

SURGERY

UNDER THE CHARGE OF

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The Reinforcement of the Pelvic Suture in a Pyelolithotomy by a Pedunculated Flap from the Fibrous Capsule of the Kidney.—Payr (*Zentralbl. f. Chir.*, 1912, xxxix, 1505) for several years has been restricting the operation of nephrolithotomy in favor of pyelolithotomy. It is becoming established that it is best to adapt the operation to the individual case rather than to employ one method for all cases. Factors which will determine the operation to be done are: The situation, size, and number of the stones present; the topography and size of the pelvis of the kidney, since in some cases inflammatory changes about the kidney prevent its being delivered; the presence or absence of an infection of the calculous kidney; and whether a unilateral or bilateral lithotomy is necessary. The objections to a nephrotomy are, chiefly, the anatomical and functional damage done to the organ, and a dangerous hemorrhage which may call for a nephrectomy. The chief objec-

tion to a pyelolithotomy is that, occasionally, the wound in the pelvis gives rise to a chronic fistula. A second objection is that the exposure and removal of the stone embedded in the calyces and parenchyma of the kidney are faulty. These difficulties, however, are experienced with a nephrotomy. After the latter operation, extensive infarction and necrosis may occur with considerable reduction in the functional value of the organ. In the greater number of pyelolithotomies, smooth healing occurs. It is very likely that in the earlier cases an overlooked stone in the lower segment of the ureter, was responsible for the persistency of the fistula. Strictures and kinking of the ureter favor it also. When a pyelolithotomy is done for the removal of the stone, in approximately aseptic cases, the wound in the pelvis should be closed immediately with an exact as possible continuous suture. This necessitates a certain degree of mobility of the kidney, so that it can be brought into the wound. It is frequently recommended to suture the pelvic wound in two layers, and to cover the wound by suturing over it the surrounding fatty and fibrous tissue. But under normal conditions the material is not suitable for such a procedure, while in the presence of inflammation or abscess, it will be much worse. In several cases Payr has employed a flap of the fibrous capsule of the kidney to cover over and reinforce the suture of the wound in the pelvis. In one case there were one large and several small renal calculi in the right kidney. The urine was purulent, and the right ureter was inactive, chromocystoscopically. The walnut-sized stone was delivered with some difficulty, and a projection on it produced a small perforation in the very weak pelvic wall, to one side of the longitudinal incision. After the removal of the remaining calculi and cleansing of the cavity, the incision was sutured in a double layer (catgut and silk), and the sclerotic and irregular fatty tissue was brought over the lateral perforation. A large right-angled flap of the fibrous capsule, of two finger's breadth, with its pedicle at the hilum, was lifted and turned over on the pelvis, and beginning of the ureter It was made to apply itself around them, and was fixed in position by a number of fine cat-gut sutures. Notwithstanding the unfavorable inflammatory conditions for making the closure water-tight, healing occurred without leakage and without reaction. The patient left the hospital in twenty-one days.

The Principles Underlying the Surgical Treatment of Gastro-intestinal Stasis, Due to Causes other than Strictural or Ulcerative Conditions.—COFFEY (*Surg., Gynec., and Obst.*, 1912, xv, 365) presents an exhaustive study of this condition. He says that there is a direct relation between gastro-intestinal stasis and abdominal ptosis, which is purely physical and mechanical. Mechanical obstructions always occur at the point of junction of a fixed and movable part of the intestinal tube, except when due to inflammatory adhesions. In 20 per cent. of human beings the ascending and descending colon have a mesentery like that of the quadruped, except at the flexures where the colon is usually attached to the front surface of the kidneys. In these defective persons the colon, instead of resting on a shelf or decline above the psoas muscle, is suspended by a direct drop from the kidney. All cases of floating kidney, mobile cecum, and general

visceroptosis, are found in this defective one-fifth of the human race. Midline ptosis produces stasis only when the normally fixed points at the second portion of the duodenum, or at the hepatic or splenic flexures, or both, remain fixed. Therefore, midline ptosis producing stasis, not only is no part of a general ptosis, but cannot exist with a general ptosis. As a rule, it is independent of any other form of localized ptosis. It is an acquired condition resulting from the combined effects of a chronically loaded colon or an overdistended stomach plus long-continued or severe exercise, or occupations requiring long standing, which stretches the normal supports. General visceroptosis is probably impossible in normal individuals having perfect fusion of the ascending and descending colon with the parietal peritoneum, which explains the fact that the great majority of individuals will not develop ptosis, no matter how thin they become nor how flabby their abdominal muscles become. The large majority of ptoses may be successfully treated, and the patients made comfortable by medical and dietary measures. Surgery should never be considered for the treatment of ptosis *per se*. Given a case of right-sided ptosis with a moderately movable right kidney, painful cecum and appendix, not relieved by medical measures, the proper treatment is removal of the appendix and fixing the ascending colon through a right rectus incision, plus fattening. This will be sufficient to retain the kidney in position. If the right kidney is exceedingly movable, and the symptoms demand surgical relief, the appendix is removed and the colon and kidney both fixed through a posterior incision. A coexisting pericolic membrane may or may not be removed, according to the judgment of the operator at the time. Usually Coffey has not removed it. An operation which fixes a floating kidney without fixing the colon at the same time is not a sound surgical procedure. A mobile cecum, with or without the membrane in which the hepatic flexure remains fixed is best treated by fixing the cecum and ascending colon to the parietal peritoneum. Midline ptosis of long standing not relieved by proper medical treatment, is successfully treated surgically by shortening the ligaments of the liver and stomach, suturing the omentum to the abdominal wall, and expanding the upper abdomen. The results following this method of treating midline ptosis with stasis are fully as striking and complete as those produced by a gastro-enterostomy for mechanical obstruction at the pylorus. Sigmoid ptosis, producing severe stasis, can only be treated successfully by short circuiting or excising. General visceroptosis, the pathognomonic sign of which is a floating left kidney, is not a surgical condition. Such patients may be materially benefited and made very comfortable by wise medical treatment combined with Martin's gymnastic treatment, but they can never be made normal individuals. The only hope for successful surgical treatment of general ptosis must be in the line of a prophylactic or orthopedic operation, which may be made possible in the future by improved diagnostic technique which will enable the doctor to determine the cases of movable colon in the feeble child before the ptosis habit has been formed; in which case the defect may be remedied by fusing the ascending colon to the parietal peritoneum, just as we now repair a congenital hernia or a cleft palate. In all of his early work, including the very first case of the surgical treatment of ptosis,

Coffey has kept his patients on the back in the Trendelenburg position for at least four weeks after operation, using practically the same position as has been recently so well described by Franklin H. Martin. Coffey concedes that in bringing forward this subject of stasis and ptosis there is being opened up one of the most dangerous fields for surgical abuses that has ever been opened to the surgical "confidence" man, who needs no other excuse for performing a surgical operation than the consent of the patient. *X*-ray observation, while of inestimable value in the study of these cases, is the most dangerous agent yet placed at the disposal of the unscrupulous surgeon, because it is so convincing to the laity, and at the same time so meaningless when considered independently of the history of the case, and not properly interpreted.

External Anthrax in Man.—HEINEMANN (*Deutsch. Zeitsch. f. Chir.*, 1912, cxix, 309), after a critical study of the various methods of treatment, based upon his own material and statistics of 2000 cases, says that conservative and operative methods of treating anthrax are both rational, although, according to theory and practice, the operative is the better method. The operation must consist in a radical destruction of the carbuncle. The local therapy is to be combined with serum, salvarsan, and collargol therapy, when general infection threatens or is present. The statements concerning the damage done by the operation, are to be ignored. Only an incomplete operation can do damage. A complete operation can only do good.

The Treatment of Fistula in Ano.—ELTING (*Annals of Surgery*, 1912, lvi, 744) for a number of years has been trying to perfect a method of operating on this condition which would at the same time insure healing of the fistula within a reasonably short time, and leave the patient with as nearly a normal rectum as possible. He has made a careful study of more than 100 consecutive cases of fistula in ano. He finds that probably not more than 10 per cent. of fistula in ano are tuberculous, and that a great majority of these are secondary to demonstrable lesions elsewhere in the body, usually in the lungs. The great majority of fistulæ in ano originate from a diseased condition of the rectum, existing in the lower one and one-half inches, and that the diseased condition is usually a hemorrhoid. The operation which he performs is done as follows: He first dilates the rectal sphincters, laterally, as this has been shown to produce less disturbance of the bladder function than when done anteroposteriorly. With a probe the general course of the sinuses is located, and the communication with the bowel determined, if one is demonstrable. A circular incision at the junction of the skin and mucous membrane is made, and the bowel dissected away from the external and, if necessary, internal sphincters, which are carefully pused upward and away from all possibility of injury. The dissection of the bowel is continued upward until well above the level of the internal opening, if one exists, or to the attachment of the levator ani muscle if no internal opening can be demonstrated, care being taken to keep as near the mucosa as possible. In this way complete separation of the fistulous tracts from all communication with the bowel is effected. The external fistulous opening or openings are then somewhat enlarged, and with a small curette all

the demonstrable fistulous tracts are carefully curetted. Counter openings in the skin are made in tortuous complicated fistulous tracts if necessary. With interrupted silk sutures, the bowel, mobilized and cut off above the level of the internal fistulous opening, is approximated to the skin at the anal margin, the sutures being placed in such a way as to obliterate all dead space. The fistulous openings are lightly packed with gauze, and a rectal plug is inserted for a few hours to control oozing and insure approximation of tissues, and the operation is completed. The fistulous openings are kept open with gauze for a few days and then allowed to take care of themselves, no particular treatment being required after the first week or ten days. The bowels are moved with a mild cathartic at the end of forty-eight hours, the silk sutures come away of their own accord. Of the 105 consecutive operated cases upon which this report is based, in practically all in which it has been possible to trace the subsequent history of the patients, and in all of them, so far as Elting has been able to determine, the fistulæ have healed and remained well.

A Plastic Operation on the Dura Mater by Using the Fascia Lata for Grafting Material,—MAUCLAIRE (*Archiv. gén. d. Chir.* 1912, vi, 1, 1172) reports a case of a gun shot wound of the right fronto-temporal region in which the ball lodged itself near the occipital bone, a little to the left. A trephine opening was made and this was enlarged a little by forceps. Several attempts to feel the ball by an exploratory needle failed. After a second *x*-ray was taken a second operation was done eight days after the first, when the ball was easily and rapidly removed. But in the two operations the dura mater had been much lacerated, and it was found impossible to suture its margins together. A fragment of the fascia lata, 4 cm. long and 4 cm. wide, was removed with a little of the muscle attached, and laid over the breach in the dura mater, between it and the bone. Then the button of bone removed by the trephine was reapplied over the whole. No drainage was employed. Healing was regular and no abnormal prominence resulted.

Concerning the Value and Character of the Cammidge Reaction in Pancreatic Diseases,—MAYESIMA (*Mitt. a. d. Grenzgeb, d. Med. u. Chir.*, 1912, xxv, 403) says that the diagnosis of pancreatic diseases in life is often very difficult and in many cases is almost impossible. He concludes that the Cammidge reaction possesses no diagnostic importance in pancreatic diseases. The crystals which he obtained in his examinations were not always of the same chemico-physical character. Consequently the basic substance for the osazon crystals cannot be uniformly the same. The melting point and the estimated contained crystals show that the normal acids of the urine will cause a failure of the Cammidge reaction in most cases. From the treatment of the urine with the tribasic acetate of lead, according to Cammidge's advice, the glukoron acid cannot be completely removed. The Cammidge body is neither phenylhydrozin combined with lead, nor glukosazon, as maintained by Ham and Cleland, and Schumm and Hegler. In the formation of the crystals, pentosane may precipitate, as Cammidge said, as well as other little known carbohydrates.

An Experimental Contribution on the Formation of Venous Capillaries in the Kidney.—Isobe (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, xxv, 415), in a previous paper, studied the formation of the arterial capillaries in the kidney after implanting a portion of the omentum in a wound made in the kidney, or after surrounding a decapsulated kidney with omentum. In the venous experiments, which were done chiefly on rabbits, after a variable period following the attachment of the omentum to the kidney, the renal vein of that kidney was divided between double ligatures close to its entrance into the inferior cava, and finally the opposite kidney was extirpated. After the death of the animal the vessels were studied chiefly from the effects of venous stasis. The normal collateral venous capillaries are too scanty, at least in rabbits, to permit a compensation for the stasis in the kidney produced by ligature of the renal vein and a reestablishment of the circulation. Not one of the animals survived extirpation of one kidney with ligation of the vein of the other kidney and attachment of omentum to it after decapsulatation. When the decapsulated kidney was surrounded by omentum, the venous capillaries became more distinct than in the normal, so that the intense stasis of the cortical substance is quickly compensated for and the renal elements return to their normal condition in a short time, even when the medullary substance is mostly degenerated. In favorable cases, in which the collateral vessels are very well developed, complete restitution may follow, so that the animal tolerates well the extirpation of the opposite kidney. After implantation of the omentum into the nephrotomized kidney, the collateral venous anastomoses between the omentum and kidney are produced incomparably more quickly and abundantly than after decapsulation and surrounding the kidney with omentum. Thus not only the cortical substance but the medullary, fifteen days after the ligature of the renal vein, show their normal characteristics and the animal, notwithstanding the short time between the first and second operations or between the second and third operations, tolerates easily the extirpation of the other kidney. This cannot be said of the animal in which the kidney has been decapsulated and surrounded by omentum. In Isobe's opinion, the decapsulation and the surrounding of the kidney with omentum, still more the implantation of the omentum into the nephrotomized kidney, is a more effective operation for ascites than the Talma-Drummond operation, because the venous collateral anastomosis in the latter, between the omentum and the peritoneum poor in vessels, will not produce as good results as that between the omentum and the kidney which is very rich in vessels. A short time before a colleague employed the method and obtained a very considerable diuretic effect.

The Treatment of Gastroptosis by a Wedge-shaped Resection of the Pars Media of the Stomach.—Schlesinger (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, xxv, 527) says that operation for gastroptosis today is frequently not undertaken because the condition is looked upon only as a part of a general enteroptosis and because the correction of it alone can accomplish little. Further, the usually employed artificial elevation of the stomach does not remove the conditions accompanying ptosis, especially not the dilatation and atony, and finally

the actual good results from the known operative methods are minimal and of short duration. He objects to the Rovsing operation particularly because of the adhesions between the stomach and anterior abdominal wall, which cause pain and interference of function. His objection to the Beyea operation, which elevates the stomach by shortening of the gastro-hepatic omentum, because of the failure of the thin, friable lesser omentum to hold the sutures, and the tendency of the shortened omentum to stretch again under the weight of the stomach. He excised a portion of the pars media with the purpose of bringing the stomach back to its normal size and shape. He says that among the gastroptoses are a small number of advanced cases, which resist all internal therapy. When careful clinical observations show that the essential symptoms are actually gastric and are not due to the general asthenia, and when the disturbances are very severe and are not relieved after years of continuous internal therapy, then operative treatment is indicated. The operation proposed by Schlesinger is particularly indicated, because it gives rise to no adhesions. The wedge-shaped resection of the pars media of the stomach, which is most affected by the atony and is therefore functionally the weakest, accomplishes the purpose best, and removes about a third of the stomach, By the removal of this almost inactive portion, the emptying of the stomach will be much improved and the pressure on the transverse colon, which is the chief cause of the obstinate constipation, will be removed. The stomach itself will be restored to almost its normal working condition, and simultaneously the other abdominal organs which suffer from the unusual displacement of the stomach or from the traction on it, will be brought into more favorable relations. By observing the proper indications complete removal of the gastric disturbances is possible without causing other disadvantages.

THERAPEUTICS

UNDER THE CHARGE OF

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The Treatment of Leukemia and Pseudoleukemia with X-rays.—STENGEL and PANCOAST (*Jour. Amer. Med. Assoc.*, 1912, lix, 1166) have observed the effect of *x*-ray treatment on over 40 cases of leukemia. The first 2 of these were treated throughout by the older method of directing the applications mainly or entirely to the enlarged spleen, before the adoption of the present technique. The results were the usual unsatisfactory and disappointing ones. In the other cases the present technique, that of directing the radiation primarily to the bones, has been employed throughout, with a few exceptions.

They have no doubt as to the superiority of the results derived by the method now employed. In a few instances it has been possible to compare the results of both in connection with the same cases in which splenic radiation was instituted with either little or no benefit, or the patient made worse; but following the change to bone radiation, a decided improvement soon became manifest. They do not believe that leukemia can be permanently cured by radiation, but they do believe that the *x*-ray will do more toward prolonging life during a period of comparative comfort than any other therapeutic agent yet employed. They emphasize certain features of the general technique that has been previously described in detail. (1) The application should be made systematically to the bones of the entire body, with the exception of the head, the body being mapped into definite areas for this purpose. (2) Exactness in dosage is always most important. It should be so regulated as to produce the necessary effect without inducing toxemia, if possible. (3) The frequency of the applications is equally as important. They should be made daily when possible, and prolonged periods of rest should not be permitted. (4) Direct exposure of the spleen and other secondary enlargements should be carefully avoided during the earlier part of the treatment; this applies especially to the very large spleens of the myelogenous form of the disease. (5) Applications should not be discontinued or lessened in frequency until normal conditions prevail, or as near normal as possible. (6) The leukocyte count and especially the differential count are the most important guides for continuing or stopping the treatment. (7) Arsenic is frequently a valuable adjunct to radiation, and should be used when there is a decided anemia or when the leukocyte count remains stationary for sometime at a comparatively high figure. (8) All precaution should be taken to avoid an *x*-ray dermatitis. (9) Radiation is contraindicated in practically all cases of acute leukemia, as it will only hasten death. In acute exacerbations of chronic cases the dosage should be much reduced, and the applications should be limited to the extremities until there are some definite signs of improvement. With reference to pseudoleukemia, Stengel and Pancoast state that in a small percentage of cases in which the enlargements are localized, apparent cures result from the *x*-ray treatment. The majority of cases improve under radiation, and they believe that constant treatment often will keep these patients alive and comparatively well for years. Another small group of cases do not respond at all to the treatment, and some of these may even be rendered so toxic as to necessitate its discontinuance.

Vegetable Days in Treatment of Diabetes, Gout, and Obesity.—Disque (*Therapie d. Gegenwart*, 1912, liii, 477) advocates a restriction of the diet to vegetables once or twice a week in patients whose diets cannot be constantly controlled. These vegetable days are useful not only in diabetes and obesity, but also in gout. When ordered for gout, purin-free vegetables and fruit must be specified; spinach, peas, and beans are rich in purins. The restriction of the diet to vegetables amounts practically to starvation, but the patients do not suffer from hunger on a liberal vegetable diet. Two such vegetable days a week will reduce the number of calories considerably, with a minimum amount of discomfort to the patient.

A Case of Obstinate Hemorrhagic Diathesis Cured by Injections of Defibrinated Blood.—Rubin (*Münch. med. Woch.*, 1912, lix, 2171) reports the case of a woman, aged fifty years, with marked hemorrhages and extravasations of blood from both skin and mucous membranes. The patient's general condition was growing rapidly worse when Rubin injected 40 c.c. of defibrinated blood. The hemorrhages stopped the same day, and since then there has been no further manifestation of the trouble. She was given two subsequent injections of 40 c.c. of defibrinated blood to ensure against a relapse. This patient had previously been treated by the usual measures applied in hemorrhage such as calcium chloride, gelatin by mouth, and by subcutaneous injections, local styptics, etc., without the least influence on the bleeding. The rapidity with which the extravasations of blood disappeared was very striking. Marked metrorrhagia for a period of five months was a prominent symptom in this case, and the author suggests that this method may be valuable in the treatment of gynecological affections accompanied by hemorrhage.

Favorable Action of Salvarsan in Tabes Dorsalis.—Leredde (*Münch. med. Woch.*, 1912, lix, 2040 and 2112) believes that salvarsan exerts a most favorable action upon the course of tabes. He believes that there is no doubt that it prevents the progression of the disease and, furthermore, that it can cause the retrogression of certain lesions in the spinal roots or in the cord itself. Leredde has observed for two and one-half years a series of patients with tabes that were treated with salvarsan. A few patients were completely cured by the remedy, and in the majority of the cases the most marked symptoms have almost entirely disappeared or have become greatly improved. Leredde advises giving salvarsan in doses of 0.01 gram or neosalvarsan in doses of 0.015 gram per kilo of body weight. The treatment must be persisted in until the patient presents absolutely no symptomatic evidence of an active syphilis and until the positive Wassermann reaction entirely disappears.

The Excretion of Formaldehyde by the Kidneys of Patients Taking Hexamethylenamin.—L'Esperance and Cabot (*Boston Med. and Surg. Jour.*, 1912, cvxvii, 577) have applied Burnam's test for formaldehyde to the urine of over 250 patients taking hexamethylenamin, and their results are largely confirmatory of Burnam's findings. They believe that formaldehyde, to be of value as a urinary antiseptic, must be present in a concentration of 1 to 5000 or 6000. The results of 250 urines were that 130, or 52 per cent., showed the presence of formaldehyde. The reaction of the urine was of no importance. Some alkaline urines gave marked reactions for formaldehyde. Alkalies taken with or in combination with hexamethylenamin have no effect either in retarding or in hastening the excretion of formaldehyde. The duration of excretion of formaldehyde after a single dose of hexamethylenamin is from four to six hours, and therefore the remedy should be repeated at these intervals to secure the constant presence of formaldehyde in the urine. An increase of dosage does not affect the excretion of formaldehyde in negative urines. Patients not excreting formaldehyde do not have untoward symptoms, either bladder or

renal, regardless of the amount of hexamethylenamin taken. The chief conclusion to be drawn from the observations as related is that the urine of all patients taking hexamethylenamin should be tested for formaldehyde, and if not present, the drug should be discontinued as useless.

Experimental Pneumococcic Meningitis and its Specific Treatment. —LAMAR (*Jour. Exper. Med.*, 1912, xvi, 581) found that virulent pneumococci injected into the cranial or spinal cavities of monkeys produce constantly a meningitis closely resembling pneumococcus meningitis in man, except that the experimental disease pursues a more rapid course to the invariable death of the untreated animal. An homologous immune pneumococcus serum injected into the spinal canal exerts a restraining influence upon the disease to the extent that when employed early it prevented, exceptionally, the occurrence of infection, and thus saved the life of the animal and when given later it at first retarded the disease, but subsequently exerted no beneficial action, and was powerless to save life. A mixture of sodium oleate, immunal serum, and boric acid exerted regularly a more powerful action than immunal serum alone, and not only prevented the occurrence of infection, but also, when administered repeatedly, arrested the progress of an actually established infection, and led, often, to the enduring and perfect recovery of the inoculated animal. It is proposed to employ a similar mixture in the direct treatment of pneumococcic meningitis, and possibly of still other accessible local pneumococcic infections in man, because an anti-pneumococcus serum is at best active only against the homologous organisms or organisms the types of which have been employed in its preparation. Under the best experimental conditions the extent of its efficiency is confined within a brief space of time; therefore, the outlook for its successful employment alone in spontaneous disease is not encouraging.

An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds. —BURNAM (*Arch. Int. Med.*, 1912, x, 324) believes that the efficacy of hexamethylenamin and allied compounds as a urinary antiseptic is probably dependent upon their decomposition and the liberation of free formaldehyde in the urine. He describes a simple test for formaldehyde that may be applied to various body fluids. The test is delicate, down to 1 to 150,000 or less, and the amount of formaldehyde may be roughly estimated qualitatively. Former tests have not differentiated between hexamethylenamin and free formaldehyde. Experiments related by Burnam showed that hexamethylenamin solutions had no bactericidal effects, but that solutions of formaldehyde up to 1 to 20,000 had distinct bactericidal properties. A solution of 1 to 5000 formaldehyde destroyed the typhoid bacillus and the streptococcus within twenty-four hours. The clinical results obtained have conformed in every way with the assumption that it is the free formaldehyde which is the effective agent, and that it must be present in fairly strong solution. In not a single case has there been observed the slightest improvement from giving hexamethylenamin when the urine showed hexamethylenamin, but not free formaldehyde. Burnam found that in some patients it

was possible to secure concentrations of from 1 to 5000 of formaldehyde, and was stronger in the urine after the administration of hexamethylenamin. An important finding was that on the customary doses, of from 5 to 10 grains, given three times a day, not more than 2 patients out of 10 showed any decomposition of the drug into formaldehyde. He states further that, while not more than 10 per cent. of those examined showed the formaldehyde present after the smaller doses, at least 60 per cent. showed it when the dosage was made from 20 to 30 grains, repeated every four to six hours. In a few instances in which the formaldehyde was not present after dosage of 30 grains, the quantity was raised to as high as 100 grains at a single dose without causing a decomposition of the hexamethylenamin. The only toxic effect due to hexamethylenamin is occasioned by the liberation of free formaldehyde in the urine, and when this does not occur, it is safe to push the dose until it does appear. The proper treatment is to give a dose just large enough to be under that necessary to cause bladder irritation. Burnam says that examinations of the bile, sputum, saliva, and cerebrospinal fluid shows that even after rather large doses of hexamethylenamin, there appears in them but traces of the drug, certainly in percentages less than 1 to 150,000. Whether this trace is of hexamethylenamin, as seems most likely, or of formaldehyde, it is impossible to state, because the only test which would show it is Hehner's, which does not differentiate these two substances. So far as any therapeutic value is concerned, it does not make any difference because, as already shown, solutions of formaldehyde of the weakness indicated, do not possess any antiseptic value. Burnam believes, therefore, that the use of hexamethylenamin for the curing or bettering of, or as a prophylactic against infections of the bile passages, respiratory passages, and cerebrospinal system is illusory, and cannot possibly yield results. He has no explanation to offer for the reported clinical and bacteriological improvements, for, with the exception of the urine, he has not tested this side of the question. In the urine the clinical and bacteriological findings indicate that only those patients who show free formaldehyde have been improved by the drug. The phenylhydrazin-nitroprusside test is simple, and when applied gives the physician an easy method of determining the dose of hexamethylenamin which he should use, and also shows those cases in which no results from this drug can be expected. The test is of value in determining the efficiency of compounds whose value rests on the liberation of free formaldehyde, and it is to be hoped that an endeavor will be successful in securing a substance which, when taken by the mouth, will be excreted through the kidneys and will liberate formaldehyde in the urine in every case. Although it has its limitations, Burnam's experiences show that hexamethylenamin, when properly given, in more than half the cases of urinary infection is of immense value, and at the present time superior to any other drug in common use.

The Treatment of Epilepsy by a Diet Low in Salt.—Ulrich (*Münch. med. Woch.*, 1912, lix, 1947, 2007) reports in detail the results of treating 15 cases of epilepsy by a diet low in salt in combination with the bromide treatment. He has observed these patients con-

tinuously for a period of five years, and the improvement has been constantly maintained. He noticed immediate improvement upon the withdrawal of sodium chloride from the diet. In 6 cases the attacks ceased completely; in the other 9 there was marked improvement. The convulsions not only disappeared, but the mental conditions of the patients improved, and in no case was any marked mental deterioration observed which is so common in epileptics treated with bromides. The antagonism of chloride to bromide has been established by many experiments, and Ulrich's clinical observations indicate that bromide treatment of epilepsy is much more satisfactory when the salt content of the diet is reduced. Ulrich gives the details of a method to facilitate the use of a salt-poor diet and to make the diet less monotonous for the patient.

PEDIATRICS

UNDER THE CHARGE OF

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Appendicitis in Children.—ALEX. MITCHELL (*British Jour. Child. Dis.*, 1912, ix, 355) contributes a study of 40 consecutive cases of appendicitis in children, in which the condition was acute, and the disease had extended beyond the peritoneal covering of the appendix resulting in gangrene, peritonitis or pus-formation. Most writers now agree on the need of early surgical treatment in young subjects, in which class the disease is especially treacherous and fatal. In the present series the youngest case was aged fourteen months, and the oldest fourteen years. The average duration of illness was five days. Nausea and vomiting were not prominent in all cases, but abdominal tenderness and rigidity were present at some stage of every case. In about 6 per cent. of the cases a definite history of a previous attack was obtained, but a larger proportion gave the history of previous, continued "stomach-ache." In 9 cases a large, walled-off abscess was found. Three of these cases died, and 5 of the remaining 6 had secondary operations for removal of the appendix. In 5 cases the abscess was localized, but the peritoneum had to be opened to reach the abscess. One of these cases died. In the remaining 26 cases no definite adhesions walled off the appendicular area. In 18 of these cases there was a diffuse peritonitis and a gangrenous appendix in all but one. Six of these cases died. The remaining group include 8 cases which showed a gangrenous appendix, but little or no peritonitis. All these recovered. In this series of 40 cases the mortality was 25 per cent. On the other hand, in all the cases operated on over the same period of two years in the acute stage, before the infection had visibly extended beyond the peritoneum of the appendix, no life was lost. Appendicitis in children is a dangerous and deceptive condition,

as the stage of the disease is difficult to determine. Children are poor subjects for acute septic infection of the peritoneum, the appendix is often in a high position, and adhesions are not readily formed. The safest course in children is not to be too confident of one's power to estimate the exact condition of the appendix, but to make a definite diagnosis of the disease at the earliest stage of its course, so that prompt surgical treatment may avert a fatal conclusion.

Saline Solutions in Epidemic Diarrhea.—J. Ross MACKENZIE (*British Jour. Child. Dis.*, 1912, ix, 343) investigated the efficacy of injections of normal saline solution and sea water plasma in epidemic diarrhea. In 85 per cent. of the cases the routine treatment was efficacious. This treatment consisted, briefly, of gastric lavage, starvation for twenty-four hours, elimination by castor oil, bowel irrigation with normal saline solution, and castor oil, 4 minims every four hours as an astringent. In the 15 per cent. of cases resisting this treatment, the morbid conditions were: persistent vomiting and diarrhea, profound toxemia and collapse, and anuria. The daily urinary output is an index to the severity of the toxemia. Anuria is the key to the moribund condition in epidemic diarrhea, and is caused by lowering of the general blood pressure, and that of the kidneys in particular. Mackenzie is convinced that the subcutaneous injection of sea-water plasma, normal saline solution, or sterile water shows an immediate response, not from any particular or isolated constituent of the fluid, but from an increased blood pressure. This promotes an increased secretion of urine, and the passage of a large quantity of accumulated toxins. Normal saline solution and especially hypertonic saline solution acts more permanently, but not more rapidly than sterile water. This greater permanency is probably due to the saline constituents. The comparative value of normal saline solution and sea-water plasma in this condition cannot be estimated fully. Of Mackenzie's cases resisting ordinary treatment, 12 per cent. responded to injections of sterile water or saline solutions. The immediate effects of both these fluids were increased blood pressure and disappearance of diarrhea, collapse and anuria. Normal saline solution is as efficacious, if not as permanent in effect as salt-water plasma, and has the advantage of being cheap and easily available everywhere. The earliest indications of collapse call for subcutaneous injections of saline solution.

Are the Inclusion Bodies in Leukocytes Pathognomonic of Scarlet Fever.—H. BONGARTZ (*Berlin. klin. Woch.*, 1912, xlix, 2124) reports his observations in a study of 80 cases, relative to the inclusion bodies in the leukocytes first reported by Dölile as occurring in scarlet fever, and corroborated by Kretchmer of Strassburg and by Nicoll and Williams of New York. The inclusion bodies are small corpuscular elements within the protoplasm of the leukocytes and distinguished from the nucleus by being less intensely stained. The three forms usually seen are in shape similar to a coccus, a bacillus, and a crescent. From 1 to 6 bodies are usually found in one leukocyte. The other three observers tended to the belief that these bodies were usually found only in scarlet fever. Bongartz's observations aimed to deter-

mine whether these bodies occurred only in cases of scarlet fever, and whether they were pathognomonic of the disease. His examinations were always checked over and corroborated by two of his assistants. He examined 80 children ranging in age from five days to thirteen years. Of this number 59 were ill and 21 were in good health. In the 21 healthy children the inclusion bodies were present in 17 cases and absent in 4 cases. The bodies were found positive in 11 cases of scarlet fever, 6 cases of diphtheria, 4 cases of acute bronchitis, 3 cases of pertussis, 4 cases of tuberculosis of the bones, 4 cases of gastro-intestinal catarrh, 1 case of typhoid and 3 cases of catarrhal pneumonia. In some of the preparations, especially those of pertussis and tuberculosis the bodies were found in only a few of the leukocytes, but this was the only difference noted. Bongartz therefore concludes that the inclusion bodies are found in the protoplasm of the leukocytes in children generally. That they apparently increase in number and are found in almost all the leukocytes during febrile conditions. That it is not possible to consider the inclusion bodies pathognomonic for any one disease, certainly not for scarlet fever.

Some Considerations on Infant Feeding.—F. G. Crookshank (*British Jour. Child. Dis.*, 1912, ix, 31) mentions a large number of considerations affecting infant feeding, based on clinical experience. The method of inductive logic, the hypotheses based on clinical experience is preferable to the deductive plan, and the diversity of opinions in pediatrics is unfortunate. The problem of infant feeding depends on the mother's state of nutrition during pregnancy and the amount of stimulation of the maternal glands by particular substances in the diet during and preceding pregnancy. Defective suckling power is often due to a lack of "biological galactogogues." The milk of a cow fed on lush pasturage and sweet hay has more biological value than that from a cow fed on artificial fodder such as copra, etc. The peasant woman is usually chosen as a wet nurse in preference to the town-bred product, because she is efficient biologically, having lived on food which has produced her race. This suggests the importance of the biological qualities of the food of cows and other animals that supply human aliment. Practical experience shows that if the child be healthy and the cow well fed and kempt, far less modification of the milk is necessary. Wonderfully successful results have attended Dr. Langmead's plan of giving undiluted, unboiled milk with the addition of a few grains of sodium citrate. There is probably a definite correlation between artificial feeding in infancy and the functionating of the lactiferous gland in later life. Slightly diluted, unboiled cow's milk with the addition of some malted food has been of most service to Crookshank. Fresh milk can be increased in quantity from time to time until the child is taking almost undiluted fresh cow's milk. Malt helps in massing the curd, is slightly laxative, and compensates for deficiency in cream. A little Bermuda arrow-root, well boiled, and taken nearly cold is an excellent, temporary food in intestinal disorders. Veal or mutton broth thickened with arrow-root is a good substitute for milk during the hottest weeks of summer. It is better than boiled milk, if, in making the broth, the sternum and ribs of veal and mutton are first split open. A yearling, well forward with its teeth should

have food which exercises its jaws and stimulates the ptyalin and gastric juice, and should not be fed entirely on extractives such as beef tea, etc. The demineralization attendant on tuberculosis points to the value of mineral salts in food articles. One of the biological values of food, the hormonic, is very important, and mother's milk has an homologous hormonic value. Food for mother's should be least interfered with in manufacture or cooking.

OBSTETRICS

UNDER THE CHARGE OF

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Prolapse of the Placenta.—HARTMANN reports from Meyer's clinic in Copenhagen (*Monatsschr. f. Geb. und. Gyn.*, 1912, Band xxxv, Heft 5) the case of a multipara who had suffered from prolonged albuminuria following diphtheria in childhood. She was admitted to hospital about six months pregnant, with marked nephritis and edema. There had been bleeding at varying intervals. Shortly after admission the patient discharged clots with fluid blood, and examination showed the internal os covered by placenta. An elastic bag was inserted to hasten labor and check hemorrhage. The patient gradually became worse, the uterus becoming greatly distended, and edema of the genitals developing. It was impossible to deliver the bag unemptied through the cervix. On emptying and removing it, blood clots were delivered and also the placenta. On rupturing the membranes the fetus was delivered by version and extraction. The patient died, with great restlessness, dyspnea, and a pulse at first strong, then becoming weak. Autopsy showed chronic nephritis with characteristic changes in the heart and vessels. There was abundant serous fluid in the thoracic cavity, the pericardium, and peritoneum. The tissues were anemic. On examining the placenta the changes characteristic of nephritis were well developed.

The Influence of Vaginal Douches during Pregnancy upon the Normal Genital Tract.—POLANO (*Zeitschr. f. Geburts. und Gynäk.*, 1912, Band lxx, Heft 2) has made observations to ascertain the effect produced upon pregnant patients by vaginal douches. His observations were made upon patients not in labor, some of them in a normal condition, others suffering from vaginal and cervical catarrh. Various antiseptics and disinfectants were employed. He finds that one cannot accurately estimate the sterility of the birth canal by the comparative sterility of culture material used as a test. He believes that the growth of material upon agar is our most practical method of estimating the results obtained by different methods of treatment.

He finds that increased growth of bacteria uopn agar is accompanied by increased formation of epithelial cells, leukocytes, and increased development of bacteria is observed by microscopic examination. None of the antiseptics employed produced much effect upon the chemical reaction of vaginal secretion or upon the growth of bacteria. The staphylococci were especially resistant. The most efficient antiseptics were alaun, alcohol, alsol, nitrate of silver, and alum. Less efficient, but still of practical value, were lysoform, and 0.2 per cent. iodine; while acetic acid, lysol, and lactic acid, were least efficient. Apparently those antiseptics were most useful which produced a shrinking and practical drying effect upon the bacteria. In this connection, the paper of AMERSBACH, from the Bacteriological Laboratory at Frankfurt (*Zeitschr. f. Geburts. und Gynäk.*, 1912, Band lxx, Heft 2) is of interest. He examined 40 normal pregnant patients to determine the presence of bacteria in the genital tract; 81 examinations made in these cases showed cocci, which could be positively demonstrated by staining. Of these, 48 per cent. were successfully grown in culture, produced hemolysis, and by their toxins could be identified as pyogenic staphylococci. The labor and puerperal periods of these patients were normal.

The Clinical and Bacteriological Study of Abortion.—BONDY (*Zeitschr. f. Geburts. und Gynäk.*, 1912, Band lxx, Heft 2) has made an extensive study of cases of abortion to determine the presence of bacteria. He finds that in the majority of cases, especially those having fever, that the well-recognized pathogenical varieties are present. In 62 per cent. of cases having fever streptococci were found. In all cases streptococci were present in 37 per cent. More than half of those having fever, and at least one-third of all cases of abortion, showed the presence of streptococci in the genital tract. In many of these patients, in addition, staphylococci, pneumococci, gonococci, and colon bacilli, were also present, so that in 81 per cent. of fever cases, infectious bacteria were found, and in 53 per cent. of those without fever. The colon bacilli were present in 37 per cent. of abortions, and in 72 per cent. of those having fever. It is difficult to establish the distinction of putrid abortion where only the germs of decomposition are present, and septic abortion. Germs are usually found in abortion only in the superficial layers of necrotic decidua, seldom penetrating to the deeper tissues. It is important in these cases to study, if possible, the presence and multiplication of bacteria in the blood stream. Ptomaines are now held to be of little importance in these cases, and sapremic cases are now thought to be invariably accompanied by the entrance of bacteria into the blood stream. His investigations give Bondy no reason to believe that we should make essential changes in our methods of treatment at present. In all cases of abortion germs may be found in the uterus, and those methods should be employed to disinfect the uterus which are least harmful. We cannot now distinguish between bacteria which are but little harmful and those which are actively pathogenic. In many cases the fate of the patient is already decided. She is infected, or not infected, before she reaches the hands of the obstetrician. There is no reason to adopt the use of the sharp curette in attempting to empty the uterus,

and whenever possible debris should be removed by the finger or a blunt instrument. In many cases the blunt curette is far more efficient cautiously used than the finger. Each case must be studied upon its own merits, and if remedies are used to promote uterine contraction, and care is taken to avoid injuring the lining membrane of the uterus, the best results will be obtained. Pituitrin seems to be efficient in many of these cases.

Surgical Treatment of Uterine Hemorrhage Complicating Pregnancy, Labor, and the Puerperal State.—At the Sixth International Congress of Obstetrics and Gynecology, Berlin, September 9, 1912, COUVELAIRE stated that the majority of French obstetricians treated placenta prævia by rupturing the membranes, the introduction of a bag within the cavity of the membranes, or version without extraction. The use of the vaginal tampon and rapid delivery through the vagina had been abandoned. In Pinard's clinic, in twenty years, in 53,000 labors, there had occurred 162 cases of placenta prævia with 10 deaths, a maternal mortality of 6.7 per cent. Champetier de Ribes reported 67 cases with 6 deaths, a maternal mortality of 8.9 per cent. Professor Bar had 153 cases with 14 deaths, a maternal mortality of 9.2 per cent. In the Lyons Maternity, 167 cases were reported with 13 deaths, a maternal mortality of 7.78 per cent. Ferré reported 35 cases, with 4 deaths, a maternal mortality of 11.4 per cent. The average mortality of all these cases was 8.2 per cent. If those cases are subtracted which are brought to the clinic in a practically hopeless condition through severe hemorrhage, the maternal mortality sinks to 4 per cent. Septic infection is the most frequent cause of death. Next to this, acute anemia, and then rupture of the uterus; three-fifths of all cases result from infection and shock. In but 1.2 per cent. of the fatal cases was hemorrhage alone the cause of death. It is believed that the blood loss itself is not sufficiently great in many cases to justify abdominal section, and French obstetricians limit themselves to the methods of treatment already described. With these methods the mortality among the children varies from 44 to 60 per cent. This arises from the fact that most of the children are premature, and born with little power of resistance. There is little inclination in France to adopt the extraperitoneal variety of section, and in cases where section is indicated the classic method is preferred. Should the necessity for removing the uterus arise, partial or total hysterectomy is indicated. In hemorrhage from the premature separation of the normally implanted placenta the maternal mortality is 20 per cent. This is a great improvement over the old statistics, which ranged from 50 to 65 per cent. These results are still most unsatisfactory, and in cases where the bleeding is sudden and profuse, hysterectomy is the only recourse. When the abdomen is opened the operator can judge whether he can save the uterus, or whether there are injuries or lesions which make its removal necessary. In cases of uteroplacental apoplexy where the uterine wall is enormously infiltrated with blood, dissecting the muscular substance and often distending the broad ligaments, the uterus must be removed. When the cervix is hard and resisting, rapid delivery by section is indicated, and most French obstetricians prefer the abdominal route. Jung, of Göttingen, has successfully practised

vaginal section in incomplete abortion complicated by hemorrhage. Should bleeding occur during labor the patient must be delivered as soon as possible. In the absence of contracted pelvis the vaginal route should be selected. Where placenta prævia is not threatening the use of the elastic bag is indicated, and in other cases vaginal Cesarean section. The use of the bag is difficult under proper precautions in private practice. He preferred vaginal Cesarean section to abdominal, and would carefully close lacerations of the cervix occurring during delivery. In rupture of the uterus abdominal section is indicated, as the results of the tampon have been unsatisfactory. He had never been obliged to extirpate the uterus because of atony, but the possibility of this complication could not be denied. Where hemorrhage developed suddenly and profusely he had obtained good results by bimanual compression of the aorta, which he considered much superior to Gauss' instrument or Momburg's bandage. Davis, of Philadelphia, described a simple method of controlling uterine hemorrhage in accidental separation after the uterus had been emptied. The gloved hand is inserted within the uterus, folded to make a fist, and the abdominal aorta compressed through the uterine wall at the brim of the pelvis. The presence of the closed hand excites uterine contraction, and such pressure may be continued for a short time to permit intravenous saline transfusion and the use of hypodermic stimulation. It should be followed by tamponing with iodoform gauze. He also reported 7 abdominal sections for placenta prævia, three of them performed upon mothers in an exhausted condition through hemorrhage. All of the mothers recovered, and 3 of the children. One patient has since borne a healthy living child in spontaneous labor. He had abandoned the vaginal tampon because it is likely to result in infection, especially when applied by the general practitioner in private houses. A fatal case occurring in the hands of an assistant in his clinic was reported as an example. In hospital practice he believed that abdominal Cesarean section for placenta prævia is the most rapid and certain method of dealing with this complication, and also with accidental separation of the normally implanted placenta and with ruptured uterus. Such cases demand hospital care at once. In private houses version without extraction is best adapted for the circumstances present. He also calls attention to the fact that the ovum attached to the lower uterine segment and cervix in placenta prævia is as truly ectopic as the ovum which develops within the Fallopian tube and Graafian follicle. If it is rational to treat the latter by surgical interference, it is equally indicated with the former. Zweifel, of Leipzig, believed that in placenta prævia the use of the elastic bag gave better results for the child, but was more difficult and more bloody than combined version. Cesarean section he would limit to cases of full term living children, the mother in an aseptic condition, and the placenta entirely covering the os. He had operated twice with excellent results. He had been interested to observe how complete and rapid was the cessation of hemorrhage when the uterus was opened. He preferred the transperitoneal method of operation. He placed little reliance upon the iodoform gauze tampon, but he had seen good results from Momburg's bandage. In desperate cases the total removal of the unopened uterus

is indicated. He exhibited two specimens showing the entire removal of the uterus in placenta prævia. In the last four years he has operated 6 times with 3 good results. The elastic bag he considered more efficient than the tampon. In 8 cases he had used the gauze saturated with a preparation of iron free from acid, with 6 good results. Mayer, of Tübingen, calls attention to the danger attending the use of Momburg's bandage. In 1 case the patient had hemorrhage from the veins in the lower uterine segment. The spermatic vessels in this patient must have been compresesd. Experiments on animals show that by the use of this bandage the ureter may be compressed and also the renal arteries. The kidneys show distinct disturbance in function, and this is especially apt to happen in cases of nephroptosis. In latent pyelitis this would be dangerous. In some cases the action of the heart has been greatly embarassed, and in some patients the removal of the bandage was followed by threatened cessation of the heart's action. Pankow, of Düsseldorf, would distinguish two varieties of placenta prævia: Primary, where the ovum embeds itself in the isthmus of the uterus, and, secondary, where the ovum was attached to the uterine body, a portion of it extending up the isthmus. Evidently the first is the more serious variety. In both, the vessels of the isthmus become greatly dilated. As these vessels are not controlled by contractions of the upper uterine segment, it is evident that the occurrence of labor does not close these enlarged vessels. The wall of the uterus at this point is often infiltrated with fetal cells which favor the occurrence of hemorrhage. The dilatation of the lower uterine segment which occurs during labor also encourages hemorrhage, and in some cases favors rupture of the uterus. From the anatomy of the situation, it follows that that method of treatment is best which empties the uterus promptly, removing the placenta without distending the cervix and isthmus. Abdominal Cesarean section in the classic variety fulfils these indications. The average mortality of mothers in placenta prævia in various clinics ranges from 5 to 10 per cent.; the children from 50 to 80 per cent. It seems irrational to operate to save the lives of children in contracted pelvis, and to neglect the children in placenta prævia. An early diagnosis of placenta prævia can usually be made, and if these cases are sent at once to hospital they should be in a clean condition for operation. In the Freiburg clinic, in 79 cases of placenta prævia, 38 were delivered by Cesarean section, with a maternal mortality of 2.5 per cent., and a fetal mortality among viable children of 2.9 per cent.

GYNECOLOGY

UNDER THE CHARGE OF

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Transvaginal Resection of Rectal Carcinoma.—CHALIER and PERRIN (*Rev. de Gyn.*, 1912, xix, 101) think that the vaginal route, where it

can be employed, offers all the advantages of the other methods of approach to the carcinomatous rectum, and possesses some of its own in addition. It can be carried out in an equally aseptic manner, permits of as wide a resection as the other methods, and preserves the sphincteric function. Its particular advantage is that it permits of more thoroughly exploring the extent of the cancer than any other method of attack from below, the extensive opening in the vagina and perineum offering a large field of operation, without producing as much shock as the methods involving a resection of a portion of the pelvic skeleton. While fissures and stenoses may follow this, as any other type of operation, they are certainly no more frequent in occurrence, and are equally amenable to treatment. The operation finds its indication particularly in cases of limited, non-adherent tumors, whose lower limit is at least 4 or 5 cm. above the anus, and whose upper limit does not extend above the upper end of the rectum (third sacral vertebra), although in a few instances even sigmoid tumors have been successfully resected through the vagina. The chief local contraindications are vaginal malformations, inflammatory genital affections, and marked decrease in the transverse diameter of the pelvic outlet (rachitic pelves). Chalier and Perrin's technique, which differs in some points from that described by previous writers, is very briefly, as follows: The peritoneal cavity is opened by the usual transverse colpotomy incision, posterior to the cervix. The extent, operability, etc., of the tumor is explored through this opening; then a vertical incision is carried downward from the centre of the transverse one, curving gradually to the left, and being continued over the perineum to the side of the anus as a Schuchardt paravaginal incision. The rectum and sigmoid are now carefully freed from their lateral and posterior attachments, this process being carried to a point at least 2 or 3 cm. above the upper limits of the tumor, and to a similar distance below the lower limits. The peritoneal cavity is now carefully closed by suturing the peritoneum lining the anterior wall of the pouch of Douglas to the serosa of the anterior wall of the pulled-down sigmoid as far as possible above the point at which resection is to be done. The tumor-bearing portion of the gut is now resected, beginning preferably above between two ligatures, and working downward. The portion of rectum remaining below the point of resection, attached to the sphincter, is now denuded of its mucosa, and the upper segment drawn down through it by means of forceps introduced through the anus, the mucosa of this invaginated upper segment being then sutured to the peri-anal skin surface. The operation is completed by closing the perineovaginal incision, introducing a small drain into the lower angle, and into each ischiorectal fossa. The bowels are kept locked for eight to ten days. The chief postoperative complications to be feared are fistulæ and stenoses; the former are to be treated by suitable plastic operations, the latter by dilatation with Hegar's bougies. Chalier and Perrin report 2 cases operated upon by this method; the first died seventeen months after operation with generalized metastases (it seems probable that a liver metastasis may have been present at the time of operation). The second case had been done only seven weeks before the publication of the report; at that time she appeared cured, and has perfect sphincter control.

Diffuse Gonorrheal Peritonitis.—Notwithstanding the general acceptance of the fact that an ascending gonorrheal infection can produce a circumscribed pelviperitonitis, opinions still differ widely as to the ability of the gonococcus, without mixed infection, to produce a *generalized* purulent peritonitis. While many authors accept this possibility as demonstrated, others—among them such prominent gynecologists as Bumm and Fromme—deny it absolutely, holding that in every such case reported the condition was due to a flooding of the abdominal cavity with pus from an old gonorrheal pyosalpinx, and that the gonococcus can produce a generalized, purulent peritonitis only when in symbiosis with other organisms. ALBRECHT (*Münch. med. Woch.*, 1912, lix, 2268) considers that this question is now in the stage of discussion through which have passed similar ones with regard to the possibility of pure gonorrheal infections of the endocardium, pericardium, joint cavities, etc., all of which have been definitely settled in the positive. Albrecht has observed 4 cases of diffuse, purulent peritonitis, which he believes were due solely to gonorrheal infection. One of these was a girl, aged eighteen years, who was sent to the hospital with the diagnosis of general peritonitis due to a ruptured appendix. At operation the peritoneal cavity was found full of creamy pus, which showed in smears large numbers of gonococci, and no other organisms. The appendix was normal; both tubes were swollen, and exuded pus from their abdominal ends. The entire serosa was acutely inflamed, and covered with small patches of fibrin. Growth was obtained after inoculation from the pus only on Pfeiffer's blood-agar, this proving to be a pure culture of gonococci. In the other 3 cases smears showed likewise gonococci alone, but cultures were not successful. One of these cases was a male, who had contracted acute gonorrhea two weeks previously; the others were young women. In all these patients the clinical symptoms were identical; the onset was sudden and stormy, suggesting peritonitis following a ruptured appendix, which was the clinical diagnosis in each instance. In all the symptoms disappeared immediately after removing the pus from the abdomen, and the patients made an uneventful recovery, the gonorrheal type of peritonitis showing a remarkably benign course, in contradistinction to those of other origin. Albrecht considers that these cases, and especially the first one, prove conclusively that a diffuse, purulent peritonitis can arise from pure gonorrheal infection without the presence of any other organisms; he thinks that immediate operation is indicated in all instances, as it is impossible definitely to diagnosticate gonorrheal from other much more common types of peritonitis.

Internal Secretion of the Ovary.—A recent contribution to this much discussed subject has been made by SCHICKELE (*Biochem. Zeitschr.*, 1912, xxxviii, 169), who has continued his experiments with extracts of various organs obtained by subjecting them to great pressure. His first report on these experiments was made about two years ago (*Münch. med. Woch.*, 1911, lviii, 123), and has already been reviewed in this department. His original experiments demonstrated that these "pressure-extracts" all exhibit a certain inhibitory action on the coagulation of blood, but the extracts of the uterus and ovaries exert

a very much more powerful effect than those from any other organ. He also showed that these extracts, when injected into the circulation of an animal, have a distinct depressor action on the blood pressure. In his later work he has been able to show that not only do differences in this coagulation-inhibiting action exist between different organs, but that in cases showing clinically no symptoms of excessive uterine bleeding, this inhibitory power is more pronounced in the ovarian than in the uterine extracts; the organs from individuals who had suffered from severe menorrhagia, on the other hand, show a greater activity on the part of the uterus than of the ovaries. He has noted further that extracts from the uterine mucosa are always more active than those from the muscle tissue, and that the action of fibroid tumor tissue is less intense than that of the uterus itself. The inhibitory substance, which he believes to be an antithrombin, is firmly combined with the cell-tissue, probably existing as an endocellular material of some sort. Although this substance gets into the menstrual blood in large quantities, it is not found in the circulating blood even of patients whose organs show unusually marked activity. An interesting fact that Schickele has brought out is that the uterus and ovaries of women past the menopause do not show any greater activity than any other organ of the body. Since the same substance, having this anti-thrombotic action, is found in the ovaries, uterus, and menstrual blood, Schickele considers it rational to assume that the ovaries are the source of its formation; that it is secreted by them into the circulating blood, but in such small quantities as to be undemonstrable, and is then stored up by the uterus, to be excreted by it at periodic intervals in the menstrual blood. The substance, which when injected into the circulation, causes dilatation of the vessels, with consequent fall in blood pressure, is also found in the menstrual blood, as well as in the uterus, tubes, and ovaries, but this likewise disappears after the menopause. He considers it probable that this also originates in the ovaries, whence it is carried to the uterus, but has not been able actually to demonstrate this. The occasional occurrence of vicarious menstruation would seem to indicate, however, that it may at times get into the general circulation in larger quantities than normal.

Menstruation in Healthy Individuals.—In order to determine, if possible, whether the occurrence of menstruation exerts any actual, objectively demonstrable effect upon the normal female organism, as has so often been asserted, SCHMOTKIN (*Arch. f. Gyn.*, 1912, xcvii, 495) has carried out a rather interesting series of investigations. For three consecutive months she has kept careful records of the blood-pressure (systolic and diastolic), pulse, temperature, and muscular power of eight healthy young women aged from eighteen to twenty-five years, taking readings every other day, except during the menstrual period, when daily examinations were made. Her subjects for these tests were all maids employed about the clinic; their regular work had to be carried on therefore just as actively throughout menstruation as in the interval. As a result of these investigations, the individual findings of which are all tabulated in detail in the original article, Schmotkin says that she was unable to demonstrate any considerable variations in any of the factors considered in any of the subjects.

The premenstrual rise and menstrual fall in the curve representing these activities, which has been described by so many investigators was completely lacking; no periodicity in the bodily functions could be observed, so that menstruation, in these cases at least, must be considered as a completely normal process, exerting no appreciable influence on the organism as a whole.

Treatment of Sterility.—Norris (*Surg., Gyn., and Obst.*, 1912, xv, 706) reports exceedingly satisfactory results in the treatment of certain cases of sterility in women by the use of his modification of the Wylie drain. This, a form of stem pessary, having a well-marked groove on each surface, and a T-shaped lower end, the arms of the T resting against the outer surface of the cervix when the drain is in place, and being held there by silk ligatures placed through a small hole, provided for that purpose at the end of each arm, and taking in a bite of the cervical tissue. The stem, which has a bulbar enlargement on the inner end, should be of such length as to reach to within 1.5 cm. of the top of the uterine cavity. The technique employed by Norris in the use of this pessary is merely to give the cervix a thorough dilatation, taking at least fifteen minutes for this, and then to introduce the drain, after exploring the interior of the uterus for the possible presence of a polyp or small myoma. The instrument may stay in place for six weeks, during which time no douches should be taken by the patient. The presence of the drain is no contraindication to the resumption of sexual relations, however; indeed, in three of Norris' cases, conception apparently occurred while it was in place. Norris emphasizes that this form of treatment should be used only in those cases where sterility is present with no other pathological condition than a small cervical canal. Where the slightest suspicion of any inflammatory condition exists, it is absolutely contraindicated. By its use, Norris reports a cure in 13 out of 35 cases whose histories subsequent to the operation could be traced, giving a ratio of 37 per cent., but since a number of the patients in whom pregnancy has not as yet ensued have been operated on within the last year, it is reasonable to suppose that this percentage may be somewhat increased.

Occurrence of Sarcomatous Degeneration on Uterine Myomas.—An unusually high percentage of myomas showing beginning sarcomatous change is reported by Warnekros (*Arch. f. Gyn.*, 1912, xcvii, 292) from Bumm's clinic in Berlin. He has subjected their last 78 cases of myoma to very thorough microscopic examination, as a result of which he has found areas which he considers carcinomatous in no less than 7, corresponding to almost 10 per cent. He admits that this is much higher than the average reported by most observers, which at the present time appears to be about 4 or 5 per cent., and also that this series of cases is too small upon which to assume that such a high precentage of malignancy represents the true state of affairs, but he also insists upon the fact that this percentage is steadily increasing as it is becoming the routine practice of many clinics to subject all myomatous tumors to a much more thorough routine examination than formerly. These areas may be extremely small, and since they do not occur in any definite portion of the myoma, it is not

unreasonable to assume that they be frequently overlooked when only one or two small pieces are taken from a large tumor for microscopic examination. An extremely practical side to the determination of the true proportion of myomas which undergo malignant change is furnished, he thinks, by the increasing tendency, at least on the part of many of the German clinics, to subject these patients to *x*-ray treatment rather than to operation; if it can be shown that malignancy occurs in the long run in these tumors with anything like the frequency that he has apparently demonstrated, general adoption of *x*-ray therapy in place of extirpation must of necessity be associated with a very great element of danger for a considerable proportion of the patients.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Chloroma.—A. M. BURGESS (*Jour. Med. Research*, November, 1912, xxvii, No. 2) reports 2 cases of chloroma, and reviews the subject. It will be remembered that the striking characteristic of this so-called disease, which is relatively a rare one, is the greenish color of the tumor. Burgess has found some 80 cases reported. Nothing new is at hand regarding the coloring matter, which is by some supposed to be a lipochrome. The author finds that the tumors called by this name do not constitute a pathological entity, but are a manifestation of one of the types of acute myelogenous leukemia; no connection with lymphatic leukemia has yet been demonstrated. Myelogenous leukemia is thus to be considered as the metastasis in the blood of a neoplastic growth in the bone marrow, and in cases where the cells are little differentiated, their power of growth is so great as to permit definite localized masses to occur; these growths, if possessed of the characteristic green color, are designated by the term chloroma.

Smallpox.—FISCHER-DEFOY (*Schmidt's Jahrb.*, October, 1912, Band cccxvi, Heft 1) has collected current literature upon smallpox, vaccination, and kindred subjects, with the usual results; as always, it is mortifying to see the position occupied by English-speaking nations in the morbidity statistics, and to be compelled to accept the patronizing, if good-natured smile, that circumstances allow the continental nations to bestow. In Germany, during the fourteen years previous to 1910, there were 3348 cases of smallpox, of whom 27 per cent. were foreign. England's yearly death-rate, according to House of Commons statistics is 600 to 800, and the United States (possibly including Canada), in 1910 showed 30,000 cases. In Prussia in 1908, the death-rate comprised 7 per cent. of the vaccinated and 47 per cent. of the unvaccin-

ated. For one year, Bavaria shows 8 cases of smallpox, Saxony, 19. Great Britain does better for her colonies than for herself, for while in India during the seventeen years preceding 1886, 45,000 died of smallpox, in the seventeen succeeding years, 9126 died. On the European continent, Russia still shows the greatest proportion of cases, if Great Britain be excepted, and the result of vaccination in the Philippines has shown most satisfactory results.

Comparative Toxicity of Methyl and Ethyl Alcohol.—The occurrence of large numbers of fatal cases of methyl aclohol poisoning gives interest to the experiments of NICLOUX AND PLACET (*Jour. de Phys. et de Path. gén.*, September, 1912, vol. xiv, No. 5), with regard to its toxicity in comparison with ethyl alcohol. In a single large dose given intravenously methyl alcohol is the less toxic, but at death there is a greater proportion found in the blood and the tissues; of the tissues the brain is the most arid in fixing either form of alcohol. If the alcohol be ingested and repeated doses, methyl alcohol is the more toxic, because it is capable of less complete combustion, and is eliminated more slowly; a quarter of the methyl alcohol ingested is found to be in the excretions and the excretory organs. In spite of these facts, Nicloux and Placet considers that it is necessary to invoke the impurities of methyl alcohol to explain the numerous fatal cases unless it can be proved that man has a particular susceptibility to the action of the drug.

Bone Lesions in Skeletons of Ancient Peoples.—RUFFER AND RIETTI (*Journal of Pathology and Bacteriology*, April, 1912), publish the results of their examinations of ancient skeletons. The former had previously studied the histology of Egyptian mummies, and is deeply interested in the unusual field that is thus opened for investigation. Most of Ruffer and Rietti's good specimens will be placed in the Medical School Museum at Cairo, but a considerable number of bones will remain for distribution to recognized pathological institutes which may apply for the same. The earliest skeletons date from 3000 B.C., and show spondylitis deformans as well as other osteo-arthritic lesions in the hands, sacro-iliac articulations, hip-joints, and other parts. It is remarkable how numerous were the lesions of this type found in these skeletons; nor were the results very different when skeletons from the Roman period, 200 A.D., were examined, for here of 8 skeletons, no less than 4 showed marked lesions of arthritis deformans. Ruffer and Rietti find themselves unable to offer even a guess as to the etiology of these osteo-arthritic lesions. Should we ever discover more about the bacterial diseases of Ancient Egypt we shall perhaps be able to indicate the cause of this widespread disease. Ruffer and Rietti found a certain number of cases in the young, but point out that it was essentially a disease of old age, because, in hieroglyphic writing, the symbol of old age was a man deformed by chronic arthritis. Attention was paid to an attempt to determine the extent to which disease of the teeth prevailed in ancient times, and Ruffer and Rietti, after examination of a large number of skeletons, are of the opinion that there seems to have been much the same distribution of dental disease then as there is now. Although the Egyptians were learned in dentistry, there is evidence that they frequently failed to pull out teeth which prevented the exit of abscesses, for

Ruffer and Rietti have seen the results of abscesses which had ruptured through bone but for which no teeth had been removed, although such removal was most obviously indicated. No evidence is forthcoming from the present writers that the Egyptians knew anything about filling teeth, and they further state that they have only once seen ancient artificial teeth, which were found in a Roman tomb in Egypt. The contrivance consists of teeth bound together by gold wire, and was evidently for show purposes as it could not possibly have been used for mastication. The use of the tooth brush or some such instrument was evidently widespread, and the teeth in most cases showed evidence of careful attention, deposits of tartar being extremely infrequent.

The Pineal Body.—A review of the literature dealing recently with the pineal body is given in part in the *Medical Chronicle* for December, 1912, by L. J. KIDD. Some of the conclusions already made are as follows; there is a general belief that the pineal body is functional in all vertebrates and little evidence to show that it is a rudimentary, degenerated, or disappearing organ. Although there is no evidence that is sufficiently clear, it seems to be a fair assumption that it furnishes an internal secretion which probably in young birds and mammals at least, has an inhibitory action on the development of the testes and body growth, and on the appearance of secondary sexual characters. The relationship of the pineal glands to the ovaries is suggested but not yet proved: the relationship with the pituitary and the cortex of the adrenal is probable, but is yet uncertain. Involution of the pineal body occurs normally at puberty, but it is likely that the organ has other functions than these prepuberal effects. The histology of the organ with its neuroglial and connective tissue elements suggests definite specific function apart from that already stated.

Studies upon Pneumococcus.—From the Hospital of the Rockefeller Institute (*Jour. Exp. Med.*, November 1, 1912), comes an interesting series of studies upon pneumococcus to which brief reference may be made. COLE has studied the toxic substances produced by the pneumococcus, with the result that he finds that filtered blood serum of strongly infected animals is itself not necessarily toxic. Extracts from the organisms kept in salt solution for varying periods of time do not prove to be uniformly toxic, nor has Cole been able to discover the exact circumstances under which they prove so. Deaths from injection of such solutions suggested the results seen in acute anaphylaxis. The peritoneal washings of infected guinea-pigs injected into the circulation proved fatal in a considerable percentage of all cases, the symptoms again being those of acute anaphylaxis, which form of death becomes all but an absolute certainty when pneumococci are dissolved in solutions of bile salts and injected intravenously, a result which is probably due to the setting free of substances from the bacterial bodies in the rapid solution which the pneumococci undergo in bile at body temperature. DOCHEZ has examined the protective substances to be found in the serum of patients recovering from pneumonia. He finds that the appearance of protective bodies in the blood may coincide fairly well with the time of crisis and the disappearance of symptoms. While they are not measurably in the blood before

crisis, they may be proved in considerable quantity subsequent to that phenomenon, and yet in some cases it is impossible to demonstrate them at any period of the disease. When the serum has been tested against its homologous strain of pneumococcus most cases show that it contains protective bodies, but if the test be made against stock cultures no such quality is observed. Dochez has further studied the occurrence of pneumococcus in the circulating blood and found it in approximately half of the 37 cases studied. The course of infection when the pneumococcus was found in the blood was more severe than in those in which it could not be cultivated. Seventy-seven per cent. of patients with positive blood cultures died, and 79 per cent. of patients with negative blood cultures recovered. In fatal cases where the pneumococcus was found in the blood, its numbers rose shortly before death to enormous figures; on the other hand when blood infection was not demonstrable, fatal cases were characterized by a very rapid spread of consolidation in the lungs, and Dochez considers that the symptoms of collapse which may develop on the fifth or sixth day of lobar pneumonia, often mark the invasion of the blood by the organism; or if not this, then a marked extension of the consolidation of the lung. The pneumococci were usually virulent to animals, although in some cases with recovery they seemed to possess but a relatively low virulence. Dochez tested a univalent serum against 19 strains of typical pneumococcus, and against 4 strains of allied organisms. The serum showed some protection against 12 out of the 19, but none against the allied organisms, and the majority of the successful cases showed a high degree of protection. Dochez has further published his experiments in the coagulation time of the blood in lobar pneumonia, and finds that the time is prolonged during the acute stage, returning to normal during convalescence. The lengthening of coagulation time he considers due to an increased formation of antithrombin in the liver, which organ he also considers responsible for the similar increase in quantity of circulating fibrinogen. PEABODY has studied the carbon dioxide content of the blood in pneumonia, and finds its diminution to be all but a constant feature; it tends to be lowest in bad cases and in terminal stages, but no constant relationship exists between its amount and the severity of the disease, nor does the diminution of carbon dioxide bear any apparent relation to temperature; the diminution may even persist for a considerable time after the fever has disappeared, and appears to be one more evidence of the metabolic changes existing in infections which are by no means confined to the febrile period of the disease. The carbon dioxide content of the blood ran parallel to the output of ammonia in the urine, but does not appear to have any relation to excretion of chlorine.

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